A Bibliography of Internal Medicine

COMMUNICABLE DISEASES

A Bibliography of Internal Medicine

COMMUNICABLE DISEASES

BY ARTHUR L. BLOOMFIELD, M D



THE UNIVERSITY OF CHICAGO PRESS

Library of Congress Catalog Number 58 11470

THE UNIVERSITY OF CHICAGO PRESS CHICAGO 37
Cambridge University Press London N W 1 England
The University of Toronto Press Toronto 5 Canada

Composed and printed by THE UNIVERSITY OF CHICAGO PRESS, *Chicago Illinois U S A*

PREFACE

THE surge of new knowledge in medicine has created a tremendous problem both for the student and for the practitioner The periodical literature for a long time unwieldy has now become impossible to handle The student with the shadow of the Specialty Board examinations always hovering over him tends to keep up on the new the curious and the esoteric at the expense of the fundamental and the historical In current medical writing what is referred to as the "older literature" often turns out to be that of the previous decade Few medical students nowadays (1957) remember Sir Thomas Lewis George Minot or F G Banting most of them have never heard of Von Mering and Minkowski In brief there is real danger that we shall become completely cut off from our medical past and relapse into a sort of modern Dark Age

Furthermore after many years of teaching I am convinced that some sort of historical approach some understanding of the *development* of ideas is essential for critical comprehension of a subject or of a disease What a tragic world of ignorance was revealed by the medical student who wrote in an examination that the parasite of malaria was discovered by a man called "Vivax"!

How can this situation be corrected or at least helped? It was my thought, twenty five years ago that a selected bibliography which listed the important contributions of modern medicine (nineteenth and twentieth centuries) with critical comments might be useful and might stimulate both students and doctors to further reading and arouse their interest in the events which led up to modern knowledge A start, made with typhoid fever (Arthur L. Bloomfield "A student's bibliography of internal medicine typhoid fever" Bull. Johns Hopkins Hosp 51:234 1932) was enthusiastically received by my colleagues but I was unable to go on with the project until the present time My plan was to work through the domain of internal medicine in this fashion dealing especially with those disorders whose past is long and which carry interesting historical implications the present volume is concerned with communicable disease In order to keep the mass of material within bounds I have tried to include every reference of fundamental importance but to exclude those which add nothing essentially new It will often happen therefore that the earliest article on a certain phase of the subject may be listed rather than the "best" or the most comprehensive References to the vast very recent literature the ultimate importance of which is not yet appraisable are also necessarily limited But the attempt has been made to make this bibliography within these limits definitive

It has been a problem how far to pursue a subject into the literature of the basic sciences or of collateral branches of knowledge Here the judgment of the compiler must be paramount, and I make no apology for my selections The thought has always been however that this is a bibliography primarily for clinicians and for those with a general interest in the subject rather than for specialists

Since many of the articles and books to which reference is made are in French and German as well as in English and since many articles were published in obscure or inaccessible journals I have appended abstracts containing

the substance of the material. The translations from foreign languages are my own

Nearly every item has been seen by me and in most cases has been read and collated the carelessness with which bibliographies are compiled has astonished me over and over again during this work the reviewer had obviously not checked the original but had copied the errors of others In older works especially many references are incompletely given thus creating endless labor for those looking up the original article

The order in which to place the sections on various diseases has been a problem I finally decided to put typhoid fever first as a small tribute to Sir William Osler s textbook, where through many editions discussion of this disease came first.

My thanks are due to the publishers of the various journals in which some sections of this bibliography have already appeared the Stanford Medical Bulletin the Bulletin of the Johns Hopkins Hospital the Bulletin of the History of Medicine the A M A Archives of Internal Medicine and the Journal of Chronic Diseases for permission to reprint them [1]

I am deeply grateful for the endless kindness and interest of Miss Clara Manson, librarian of the Lane Library of Stanford Medical School who allowed me to set up an office in the library building practically within the stacks Had it not been for this and for the extraordinarily complete files of the Lane Library my task would have been impossible I am also in debt to all of the library staff for their unfailing co-operation Mrs A Hoen especially pursued many an obscure reference with skill and tenacity

Thanks are due to the National Library of Medicine formerly the Armed Forces Medical Library for the loan of a number of items

Without the generous support and encouragement of the California Foundation for Medical Research especially that of Dr Jessie Marmorston I should have had even greater difficulties in pursuing the work.

Finally I have to thank my secretary Miss Jean Mackenzie for her tireless and skilful assistance at every point

ARTHUR L BLOOMFIELD

LANE LIBRARY
STANFORD UNIVERSITY MEDICAL SCHOOL
SAN FRANCISCO CALIFORNIA
December 1957

[1] Bull Johns Hopkins Hosp typhoid fever—51 234 1932
Stanford M Bull scarlet fever—10 114 May 1952 influenza—10 293 November 1952 poliomyelitis—11:79 May 1953 tuberculosis—12:217 November 1954 pneumococcal pneumonia—13 493 November 1955 syphilis Part I—14:1 February 1956 syphilis, Part II—14 77 May 1956 smallpox and vaccination—14 137 August 1956 diphtheria—14 205 November 1956 plague—15 3 February 1957 rabies—15:61 May 1957
J Chron. Dis. malaria—1:665 June 1955 brucellosis—3:203 February 1956 amebic dysentery—5:235 February 1957 gonorrhea and gonococcal infection—5:592 May 1957
Arch. Int. Med cholera—96:734 December 1955 meningococcus infection—97 79 January 1956 rheumatic fever—98:288 September 1956
Bull. Hist Med. yellow fever—30:213 May-June 1956

Section 1

TYPHOID FEVER

Artificial immunization	Refs 20 23 24 28
Bacteriology	Refs 14 15 16 17 18 21 40
Blood count	Ref 19
Carriers	Refs 32 33 39
Contagiousness	Refs 6 7 11 12
Definition	Refs 1 2 3 4 5 7 8 9
Diagnosis	Refs 25 26 27
Differentiation from typhus	Refs 8 9
Epidemiology	Refs 13 32 33 39
Etiology	Ref 14
General articles and texts	Refs 1 2 3 4 5 7 10 12 30 31 34 37
Immunity	Refs 6 7 20 23 41
Mode of transmission	Refs 11 12 32
Paratyphoid	Ref 22
Pathology	Refs 1 2 3 4 5 29 44
Treatment	Refs 35 36 38 42 45

TYPHOID FEVER

For a good review of the early literature on typhoid fever see Gay (Ref 43) It should be remembered that, up to the nineteenth century clinical medicine was dominated largely by the Galenic point of view and that fevers were thought of in terms of vague influences alterations of humors and so on Even keen clinical observers such as Huxham were so influenced by fantastic ideas of pathological physiology that their clinical descriptions while objective are largely meaningless For the most part it is impossible to determine with just what conditions the observer was dealing

1 HUXHAM John An essay on fevers to which is now added a dissertation on the malignant ulcerous sore-throat London S A Cumberlege 1782

The essay is of importance partly because it represents the contemporary point of view on fevers in general and partly because Huxham is credited with being one of the first to differentiate under the names of "slow nervous fever" and putrid malignant fever typhus and typhoid fevers The accounts are however, largely unintelligible and contain nothing definitive except perhaps the following passage from the account of putrid fever (p 96) "The Stools especially near the State or in the Decline of the Fever are for the most Part intolerably stinking, green livid or black frequently with severe Gripes and Blood When they are more yellow or brown the less Danger but the highest when they run off insensibly of whatever Colour It is likewise a very bad Symptom when the Belly continues hard, swoln and tense after profuse Stools for this is generally the Consequence of an Inflammation or Mortification of the Intestines"

2 CHOMEL, A F Des fièvres et des maladies pestilentielles Paris Crochard 1821

During the early part of the nineteenth century there arose the remarkable school of French clinician pathologists typified in the present instance by Chomel and Louis Emancipated entirely from the domination of Galenic fantasy they described what they saw in the clinic and at post mortem with amazing clarity and exactness As examples of simple but nice use of language these works remain unsurpassed in medical writing Under the heading La fièvre entéro-mesentérique" Chomel describes briefly what was undoubtedly typhoid fever and went a step ahead of his contemporaries who had already observed intestinal ulceration in association with fevers by regarding the ulcers as a feature of the disease rather than its cause His ideas on epidemiology and contagion were indefinite and he merely emphasizes the observed fact that "entéro-mesentérique" affected young people especially and furthermore those who were relative newcomers in Paris and who found themselves under altered conditions as regarded "air food drink, and occupation"

"The progress of the disease does not differ much from that of ordinary adynamic fever unless it be in respect of the following symptoms There is in the second period, pain or tenderness on pressure in the right flank diarrhoea meteorism, and on opening the body one regularly finds ulcers of the intestines

It has been alleged that the intestinal ulcers precede the febrile movement, but the facts upon which this opinion is based do not seem to us sufficient to support it" (p 187) "If one opens the intestine throughout its extent with a scissors and examines with care the alterations of which it is the seat one encounters this remarkable fact the internal surface presents ulcers the more abundant, larger and deeper the nearer they are to the cecum and its valve " (p 192) "In some cases the serous membrane is the only one which is not destroyed in others even it is perforated and the intestinal canal communicates with the cavity of the peritoneum fecal material has in this way been able to escape and give rise to an inflammation which has precipitated the end of the subject" (p 193)

Despite this admirable description Chomel was not entirely clear or complete in his definition of the disease and it remained for Louis (see Ref 5) to give a definitive description As regards differentiation from typhus Chomel states (p 189) "We will expose the distinctive signs of these two affections later" However the only subsequent passage bearing on this point deals with it indirectly and occurs in a discussion of the significance of intestinal ulcers in fevers "One cannot then, reasonably conclude that the disturbance of general function which one observes in this disease be the effect of the lesion of the digestive tube The intestinal ulcers are to putrid fever [typhoid and perhaps some other disorders] what buboes are to plague and to anthrax *and what its proper eruption is to typhus* namely one of the phenomena of the disease and not the entire disease" (p 234)

3 De la maladie à laquelle M Bretonneau, médecin de l'hôpital à Tours a donné le nom de dothinentérie ou dothinentérite par M Trousseau, D M P ancien interne du même hôpital, Arch gén de méd 10 67 169 1826

The recognition of typhoid as a definite entity was in the air for some years before the definitive descriptions of Louis (see Ref 5) and others The idea of considering fevers as manifestations of a morbid state caused by miasm atmospheric or telluric conditions was being questioned and various entities were being separated. While local and diffuse intestinal lesions were found and described in certain fevers their relation to the disease in question and to dysentery in general was not yet clear Trousseau's paper is of importance in the history of typhoid for two reasons first, because it includes an analysis (somewhat polemic in style) of the contradictory views on fevers which agitated the physicians of the time (Prost, Petit and Serres Broussais Andral, and others) and second, because it champions the priority of Trousseau's chief Bretonneau who is claimed to have clearly defined the clinical and anatomical features of typhoid under the name of "dothinentérite" as early as 1813 "He had been led to define a disease the seat of which seems to be exclusively in the glands of Peyer and of Brunner which one encounters in the jejunum ileum, and large intestine. He has outlined the symptoms has described precisely the manifestations of the malady on successive days and has summarized the diagnostic points so clearly that there are few of his pupils who do not clearly distinguish this form of entérite from all others" (p 67) There follow excellent case reports with pathological notes especially on the intestinal ulcers

4 HEWETT Cornwallis Cases showing the frequency of the occurrence of follicular ulceration in the mucous membrane of the intestines during the progress of idiopathic fevers with dissections and observations on its pathology London M & Phys J 56 97 1826

This is the first English account of typhoid which approaches completeness The clinical features are well described as are the pathological changes However the subject still remained confused and Hewett distinctly follows the French observers and does not take the lead It is not clear from his account as to how far he was convinced that typhoid was actually a specific disease rather one gets the impression that he regarded it as a reaction type of fevers in general The descriptions of cases by Richard Bright in the following year (*Reports of Medical Cases* [London 1827] I 178) certainly refer to typhoid but are also noncommittal as to the implications of the disease

5 LOUIS P Ch A Recherches anatomiques pathologiques et thérapeutiques sur la maladie connue sous les noms de gastro-entérite fièvre putride adynamique ataxique typhoide etc etc comparée avec les maladies aigues les plus ordinaires 2 vols Paris J B Baillière 1829

"In order to know how to proceed with a problem which could not be properly clarified by simple discussion I collected from 1822 to 1827 the histories of all the patients taken with acute diseases who were admitted to the Charité in the wards Saint Jean and Saint Joseph at that time in charge of M Chomel I assembled one hundred and thirty eight observations of typhoid fever of which fifty pertained to individuals who died. I have analyzed them all in order to find out which among the numerous lesions were proper to the typhoid affection and I have compared them to the alterations found as a consequence of other acute disorders in eighty three subjects whose histories I had also collected I made the same study with reference to symptoms in the patients both with typhoid and with other acute affections whether they recovered or died in brief I analyzed the visceral alterations in one hundred and thirty three subjects and the symptoms in nearly nine hundred

"I have discarded from the material the facts which seemed to lack exactness and when I drew my conclusions from the rest I had ever in mind this thought of the author of *Émile* I know that truth lies in things and not in my mind which judges them and the less of myself I put into the conclusions which I draw the more certain I am of approaching the truth " (Introduction p ix)

Upon these observations Louis based his description of typhoid (which he separated clearly from other fevers) and to which no important clinical or gross anatomical fact has since been added While the way had been prepared by others to Louis belongs the credit of the first complete analysis of the disease He recognized fully that the essential lesions were those of the intestine mesenteric lymph nodes and spleen and separated from them secondary and incidental findings The clinical picture is admirably drawn including discussions of rose spots intestinal hemorrhage and perforation With regard to etiology Louis maintains a conservative attitude and admits frankly that the cause of typhoid is unknown His statistics however confirm the impressions current at the time that most of the cases occurred in young people recently come to Paris No comments are made on the question of contagion A point of special interest is the obvious severity of the typhoid fever of Louis in contrast to that of today

The onset was usually abrupt and stormy often with chills and with the early appearance of diarrhea and stupor In almost one fourth of Louis s fatal cases death occurred as early as the second week, of "toxemia" or secondary infection and the general mortality was nearly 30 per cent Septic complications partly the result of neglect and poor hygiene doubtless were frequent including ery sipelas suppurative angina and abscesses following the application of blisters

Louis departed deliberately from the mystic traditions of ancient medicine "It is not inappropriate to remark at this point that one cannot depend upon the authority of the ancients in questions relative to the seats of disease since these questions can be cleared up only by comparison of symptoms with lesions and the ancients were ignorant of pathological anatomy Neither is it true as is often said, that facts do not grow old. Without doubt some well-observed facts do not grow old and cannot grow old but the immense majority have grown old and those which we gather today will grow old in their turn for they carry more or less the imprint of the time of its methods more exact than those of previous periods and less rigorous than those which will follow us It behooves those who devote themselves to observation to be impressed by this truth and to realize that the best work is only good in relation to its time and that it awaits another more exact and more complete" (Preface p vii n 2)

6 [BRETONNEAU] Notice sur la contagion de la dothinentérie lue à l'Académie royale de Médecine le 7 juillet 1829 par M Bretonneau médecin de l'hôpital de Tours Arch. gén. de méd 21:57 1829

While the question of the contagiousness of typhoid had been raised and supported by the observation of scattered outbreaks in rural districts it was generally held by urban physicians that the disease was not transmissible Bretonneau was one of the first to attract serious attention to the probability of contagion in a spirited address before the Academy He opens "Typhoid fever is contagious it is contagious in Paris and nowhere is it more often contagious" "Often imported into a village one sees it spread from the patient to some of the attendants It then spreads from the affected family to another and one generally observes that it is not to the nearest family but to those whose contacts have been most intimate and frequent." He proceeds to assemble many un assailable instances of spread of the disease by contagion and answers the main arguments to the contrary Bretonneau was also one of the first to insist on the immunity produced by an attack.

7 SMITH Nathan A practical essay on typhous fever New York E Bliss & E White 1824

The essay is of special importance first because it is one of the earliest accessible accounts of typhoid fever in America and second because of Smith s clear recognition of the contagiousness of the disease One regrets that the writer s hint of a subsequent enlargement of the work was never fulfilled How ever all the essential features are described. "The Typhous Fever is a disease sui generis exhibiting as little variety in the different individuals af fected by it as some of the diseases which are acknowledged always to arise from contagion" (p 15) "There is another marked point of analogy between Typhus[1] and the common contagious maladies which is that it rarely affects

[1] Probably a misprint Smith evidently meant Typhous (Typhoid)

4 HEWETT Cornwallis Cases showing the frequency of the occurrence of follicular ulceration in the mucous membrane of the intestines during the progress of idiopathic fevers with dissections and observations on its pathology *London M & Phys J*, *56* 97 *1826*

This is the first English account of typhoid which approaches completeness The clinical features are well described as are the pathological changes However the subject still remained confused and Hewett distinctly follows the French observers and does not take the lead It is not clear from his account as to how far he was convinced that typhoid was actually a specific disease rather one gets the impression that he regarded it as a reaction type of fevers in general The descriptions of cases by Richard Bright in the following year (*Reports of Medical Cases* [London 1827] I 178) certainly refer to typhoid but are also noncommittal as to the implications of the disease

5 LOUIS P Ch A Recherches anatomiques pathologiques et thérapeutiques sur la maladie connue sous les noms de gastro-entérite fièvre putride adynamique ataxique typhoïde etc etc comparée avec les maladies aigues les plus ordinaires 2 vols Paris J B Baillière 1829

"In order to know how to proceed with a problem which could not be properly clarified by simple discussion I collected from 1822 to 1827 the histories of all the patients taken with acute diseases who were admitted to the Charité in the wards Saint Jean and Saint Joseph at that time in charge of M Chomel I assembled one hundred and thirty-eight observations of typhoid fever of which fifty pertained to individuals who died I have analyzed them all in order to find out which among the numerous lesions were proper to the typhoid affection and I have compared them to the alterations found as a consequence of other acute disorders in eighty three subjects whose histories I had also collected I made the same study with reference to symptoms in the patients both with typhoid and with other acute affections whether they recovered or died in brief I analyzed the visceral alterations in one hundred and thirty three subjects and the symptoms in nearly nine hundred

"I have discarded from the material the facts which seemed to lack exactness and when I drew my conclusions from the rest I had ever in mind this thought of the author of *Émile* I know that truth lies in things and not in my mind which judges them and the less of myself I put into the conclusions which I draw the more certain I am of approaching the truth " (Introduction p ix)

Upon these observations Louis based his description of typhoid (which he separated clearly from other fevers) and to which no important clinical or gross anatomical fact has since been added While the way had been prepared by others to Louis belongs the credit of the first complete analysis of the disease He recognized fully that the essential lesions were those of the intestine mesenteric lymph nodes and spleen and separated from them secondary and incidental findings The clinical picture is admirably drawn including discussions of rose spots intestinal hemorrhage and perforation With regard to etiology Louis maintains a conservative attitude and admits frankly that the cause of typhoid is unknown His statistics however confirm the impressions current at the time that most of the cases occurred in young people recently come to Paris No comments are made on the question of contagion. A point of special interest is the obvious severity of the typhoid fever of Louis in contrast to that of today

pox are unlike the eruption of measles" and in both were different from those found in remittent fever (malaria) In regard to the clinical features "When the disease is completely formed the characters on which the distinctions between the two forms of fever rest are 1 The suffusion of the eyes which occurs in every case or nearly every case of typhus fever with the dusky red aspect of the countenance 2. The extreme stupor and inactivity of the mind even when positive delirium does not exist 3 We also observe in typhus no constant abdominal symptoms 4 If to these symptoms be added the peculiar eruption of petechiae which is scarcely ever absent in whites there remains hardly a possibility of error In typhoid fever we consider as distinctive characters the prostration the somnolence the slow development of nervous symptoms which are not so strongly marked as in typhus The abdominal symptoms are tympanites pains in the abdomen and diarrhoea The sibilant rhonchus is heard in the chest and lastly there is an eruption of rose-coloured papulae and sudamina upon the skin" He was sure that typhus was contagious but was not certain about typhoid

10 BARTLETT Elisha The history diagnosis and treatment of typhoid and of typhus fever etc. Philadelphia Lea & Blanchard 1842

While Smith (see Ref 7) Jackson, and others had written briefly or incompletely on typhoid Bartlett's book contains the first complete account of the disease in English The article of 180 pages is a masterpiece of clinical writing and includes a careful analysis of current ideas with temperate and well reasoned conclusions Bartlett accepted the idea of the contagiousness of typhoid, recognized that the cause was unknown but felt that the disease was specific, and concluded his work with this remark "which disease, thus characterized and defined differs essentially from all others in its causes in its symptoms in its lesions and is in the present state of our knowledge only to a limited extent under the influence of control of art" (p 180)

11 BUDD William. On the fever at the clergy orphan asylum Lancet, 2:617 1856
BUDD William On intestinal fever its mode of propagation *ibid* p 694.

While various writers such as Gendron and Bretonneau in France and Nathan Smith, in America had already insisted on the contagiousness of typhoid it remained for Budd to give such an impetus to the idea that it was soon accepted by many physicians His papers are convincing examples of keen observation and clear logic. Budd stressed the importance of the bowel discharges in the transmission of the disease and sensed the existence of carriers (see below) "This species of fever has two characteristics the first is that it is an essentially contagious disorder the second that by far the most virulent part of the specific poison by which the contagion *takes effect is contained in the diarrhoeal* discharges which issue from the diseased and exanthematous bowel The first case in the series may either be casual and imported or may be due to the local rekindling, through atmospheric or other changes of poison which had remained as the dormant legacy of some previous attack." He went wrong in thinking the poison might diffuse from the excreta through the air but he suggested the following prophylaxis "These measures are founded on the power

the same individual twice" (p 16) " For during the twenty five years since I first attended patients in this disease and in that time I have visited many hundreds and have witnessed its prevalence several times in the same village I have never known or heard of its recurrence in the same person (p 17) "That the Typhous Fever is contagious is a fact so evident to those who have seen much of the disease and who have paid attention to the subject that I should have spared myself the trouble of saying anything with regard to it did I not know that there are some physicians in this country who still dispute the point one, which I think can be as fully demonstrated, as that the measles small pox and other diseases universally allowed to be contagious are so" (p 11) This assertion is elaborated and supported by specific instances

8 Observations suggested by a comparison of the post mortem appearances produced by typhous fever in Dublin Paris and Geneva By H C Lombard Physician to the Geneva Hospital (communicated in a letter to Dr Graves) Dublin J M Sc, **10** 17 1836 Second letter from Doctor Lombard to Doctor Graves on the subject of typhous fever Dublin J M Sc **10**:101 1836

Lombard was thoroughly familiar with typhoid on the Continent and believed the intestinal lesion to be a constant one although the English physicians did not at this time agree with the claims of the French in regard to a specific ulceration of Peyer s patches On visiting Ireland Lombard saw cases which seemed to be the same disease but to his surprise no intestinal lesions were present at autopsy The two letters are a summary of Lombard s reflections on his curious experience he hit on the correct solution and concludes the second letter as follows "You have two different fevers one highly contagious which I may call the *Irish Typhus* and in which the cephalic symptoms predominate to the exclusion of abdominal alterations the other which is *sporadic* and most likely not so infectious and in which the abdominal symptoms are more prominent "

These letters had a great influence in stimulating accurate differentiation of typhoid from other fevers

9 GERHARD W W Art. 1 On the typhus fever which occurred at Philadelphia in the spring and summer of 1836, illustrated by clinical observations at the Philadelphia Hospital showing the distinction between this form of disease and dothinenteritis or the typhoid fever with alteration of the follicles of the small intestine Am J M Sc **19** 289 1836 *ibid* **20**:289 1837

Although typhoid was being recognized by many as a distinct entity there was still considerable confusion with other fevers especially typhus To Gerhard belongs the credit for definitive differentiation of typhoid from typhus on the basis of the cases which he studied in the wards of the Pennsylvania Hospital Gerhard had been in Paris with Louis and like other Americans who had studied abroad recognized the identity of the disease in the two continents He points out however that the British while familiar with the intestinal lesions regarded them as "a mere complication of ordinary typhus" An epidemic of typhus in Philadelphia gave him the chance to compare the two fevers The anatomical lesions "were as different as the pustules of small

gigantic scale in the phenomena and perfect accuracy in the registration of the results—three of the best of all guarantees against fallacy—were all combined to make the induction sure For the first time in the history of man the sewage of nearly three millions of people had been brought to seethe and ferment under a burning sun in one vast open cloaca lying in their midst. The result we all know Stench so foul we may well believe had never before ascended to pollute this lower air Never before at least had a stink risen to the height of an historic event. Even ancient fable failed to furnish figures adequate to convey a conception of its thrice Augean foulness At home and abroad the state of the chief river was felt to be a national reproach. India is in revolt and the Thames stinks were the two great facts coupled together by a distinguished foreign writer to mark the climax of a national humiliation Meanwhile the hot weather passed away the returns of sickness and mortality were made up and strange to relate the result showed not only a death rate below the average but *as the leading peculiarity of the season* a remarkable diminution in the prevalence of fever diarrhoea and the other forms of disease commonly ascribed to putrid emanations So that while pythogenic compounds were poisoning the air with what may be called a forty thousand fever power the so-called pythogenic fever so far from rising in proportion fell much below its average" (p 148)

The more important parts of the book however are those which deal systematically with the modes of transmission Budd showed by well-documented studies of numerous outbreaks that the bowel discharges were the main source of infection that the disease was water borne and that milk food contaminated linen and fomites in general were sources of dissemination He erred in insisting that the contagion might be air borne and that the emanations from a sewer or water closet contaminated with the discharges from typhoid patients were dangerous He insisted however on a specific virus as the *sine qua non* of typhoid and recognized the minute size of the "germ" and its capacity for multiplication

The work is a masterpiece of exposition argument, and fine rhetoric.

14 EBERTH C J Die Organismen in den Organen bei Typhus abdominalis Virchows Arch f path. Anat 81:58 1880

The discovery of the typhoid bacillus is generally ascribed to Eberth His were however by no means the first attempts to find a microbic cause and the present paper was preceded by numerous reports describing the presence of various bacteria in the tissues of patients dead of typhoid. These were for the most part obvious saprophytes or secondary invaders The technical difficulties of studies of this sort eighty years ago must be kept in mind modern methods of fixing cutting and staining had not yet been devised Eberth treated alcohol hardened tissues with acetic acid and in some cases stained with methyl violet and Bismarck brown Masses of bacteria were found in a good many cases especially in the spleen and mesenteric lymph nodes They are described as tiny rods at times with one or more sporelike bodies The description seems far from conclusive however it is likely that Eberth was dealing with typhoid bacilli at least in a good many instances The article concludes "These findings make it highly likely that the organisms found in the organs in typhoid fever stand in a [causal] relationship to the process"

of chemical agents to destroy the infectious properties of contagious poisons If it be certain that the intestinal discharges in this fever are the principal means of propagating the disease it is no less certain that by subjecting the discharges on their issue from the body to the action of powerful disinfectants they may be entirely deprived of this property" He used chloride of zinc

Budd lamented the attitude of the Metropolitan Board of Health and of the Royal College of Physicians who like the Paris academicians in Bretonneau s day opposed the idea of contagion and believed that the disease was generated by filth In describing the epidemic at North Tawton a town in which there had been no typhoid for years he points out that the lack of sanitation could not alone be held responsible for the outbreak He describes the dirty privies near the houses the dung heaps and the pigs "Nevertheless these things existed for many years without leading to any of the results which it is the fashion to ascribe to them Much there was as I can myself testify that was offensive to the nose but fever there was none In the course of time—as was indeed, sure to happen—this element was at length added and it was then found that the conditions which had been without power to *generate* fever had but too great power in promoting its spread when once the germ of fever had been introduced

Budd sustained his thesis in subsequent articles and finally gathered all his data into a book (see Ref 13)

12 MURCHISON Charles A treatise on the continued fevers of Great Britain London Parker Son & Bourn 1862

To Murchison belongs credit for the first encyclopedic treatise on typhoid fever The section on this disease which comprises some two hundred pages has in fluenced practically every succeeding account up to the present time Points of especial importance are the elaborate catalogue of the nomenclature of the disease a masterly well-documented historical sketch with special attention to the distribution of typhoid and typhus fevers in England the elaborate statistics as to geographical distribution age sex season etc the mortality statistics and the vivid and accurate clinical descriptions There are several exquisite colored plates depicting the distribution of rose spots The discussion on con tagion is of especial interest, since Murchison held out against the idea that typhoid was communicable and insisted on its origin from the emanations of sewage *In fact, he described the disease under the name of "pythogenic" fever* (arising from putrescence) Most of Murchison s arguments against contagion can be explained by the doctrine of "carriers"

13 BUDD William Typhoid fever its nature mode of spreading and prevention London Longmans Green & Co 1873

In this book already referred to above (see Ref 11) the writer collects in a definitive manner his observations on the spread of typhoid fever He levels his batteries masked by the most delicate satire at the anticontagionists and at tacks especially the pythogenic theory which carried the authority of Murchi son s support His final devastating argument against the spontaneous generation of typhoid from putrescent matter was based on the epidemiological facts of "the hot months of 1858 and 1859 when the Thames stank so badly" "The occasion indeed as already hinted was no common one An extreme case a

17 HUEPPE Fortschr d Med 4:417 1886

In reviewing an article by Von Fodor on bacteremia Hueppe states that he was able to cultivate typhoid bacilli from the urine in one of eighteen cases This is apparently the first record of a successful attempt

18 NEUHAUSS R Nachweis der Typhus Bacillen am Lebenden Berl klin Wchnschr 23:89 1886

Many attempts to demonstrate typhoid bacilli in the blood during life were reported at about this time Some of them consisted of direct microscopic study of the blood others involved cultures of drops of blood obtained by incising rose spots or other areas of skin Neuhauss by the latter procedure was apparently the first to obtain a positive culture It was not until years later when larger amounts of blood drawn from the vein were used that the procedure became of practical diagnostic value (Schottmüller)

19 TUMAS L J Ueber die Schwankungen der Blutkörperzahl und des Hamoglobingehalts des Blutes im Verlaufe einiger Infectionskrankheiten Deutsches Arch f klin Med 41:323 1887

Tumas was the first to report fairly complete studies of the blood count in typhoid fever He observed that leukopenia was almost invariably present W S Thayer (Johns Hopkins Hosp Reps 4 83 1894) made the first careful American studies and emphasized the diagnostic value of the blood count

20 BEUMER and PEIPER Bacteriologische Studien uber die ätiologische Bedeutung der Typhus Bacillen Ztschr f Hyg u Infectionskr 2 110 1887

In the course of attempts to produce typhoid fever experimentally it was found that mice which had survived an initial small dose of typhoid bacilli later survived a much larger injection The writers clearly recognized the possible application of such immunization to man although they did not pursue the subject further at the time

21 ANTON B and FÜTTERER G Untersuchungen über Typhus abdominalis Munchen med Wchnschr 35:315 1888

Futterer first cultivated typhoid bacilli from the contents of the gall bladder at autopsy in typhoid cases The identification was probably correct He points out that the bile does not seem to have an inhibiting action on these bacteria This work was the precursor of a host of studies which proved that the gall bladder was readily infected by way of the blood stream and that it was a common situation for persistence of bacilli during the "carrier state" For further references see Gay (Ref 43)

22. ACHARD Ch. and BENSAUDE R Infections paratyphoidiques Bull et mém Soc. méd hôp Paris 13 820 1896

The fact that there were a variety of organisms which resembled the typhoid bacillus was already known. Achard and Bensaude were the first however to report cases resembling typhoid from which "paratyphoid" bacilli were isolated

Priority has been claimed for the observations of E Klebs which appeared in April 1880 ("Der Ileotyphus eine Schistomycose" Arch f exper Path u Pharmakol 12 231, 1880) but while Klebs may well have seen typhoid bacilli the description is not very satisfying especially the reference to thread like forms 80 μ in length

R Koch ("Zur Untersuchung von pathogenen Organismen Mitt a d k Gsndhtsamte 1:1 1881) reports the finding in tissues of typhoid patients of bacteria which seem to correspond to those described by Eberth he suggested that Klebs s organisms were secondary invaders as he found them only on the surface of necrotic ulcers

15 GAFFKY Zur Aetiologie des abdominal Typhus Mitt a d k Gsndhts amte 2 372 1884

Gaffky s paper is a landmark in the bacteriological study of typhoid By better methods of staining bacteria in tissues he confirmed the observations of Eberth and of Koch and showed beyond question that bacillary forms were almost al ways present in the tissues of typhoid fever patients especially in the spleen liver intestinal lymphoid tissue and to a lesser extent the kidney He pointed out clearly that the great variety of bacteria found in the superficial parts of the ulcers were probably secondary and unessential and that such organisms were not found in the depths of the diseased tissues But, most important he culti vated the bacilli from the spleen on slides coated with gelatin isolated them in pure culture and described accurately various characteristics including motility He was unable to grow the organisms from stools or blood and failed to produce anything resembling typhoid fever in animals by inoculation of pure cultures in various ways although others had claimed that they had produced the disease with material from typhoid cases The review of the literature is definitive to date and analyzes the whole problem of the bacteriology of typhoid fever in a sound and temperate manner at a time when bitter struggles for priority were likely to color medical writing Gaffky was disappointed at being unable to produce the disease in animals, but he wisely concluded that this did not ex clude the bacillus as the cause of typhoid and that further observations would be necessary to settle the question

During the next few years typhoid bacilli were cultivated from blood urine stools and other material *intra vitam*. For detailed references see Gay (Ref 43)

16 PFEIFFER, A Ueber den Nachweis der Typhus Bacillen im Darminhalt und Stuhlgang Deutsche med Wchnschr 11 500 1885

Credit for first isolating typhoid bacilli from the stools is usually given to Pfeiffer The paper is of great interest because of the technical difficulties Colonies were fished from plain agar plates and identified by appearance of the growth on potato No fermentation or agglutination tests were available at that time nor had differential plates been developed It is questionable how ever whether Pfeiffer s criteria were altogether adequate and whether his diagnosis of typhoid bacilli was invariably correct

Pfeiffer is apparently the first to have cultivated the bacillus from material outside the human body

agglutination Widal added the patient s serum to broth cultures of typhoid bacilli in a proportion of 1 to 10 or 15 and incubated for 24 hours Gross flocculation was observed at the end of this time

27 GRÜNBAUM Albert S Preliminary note on the use of the agglutinative action of human serum for the diagnosis of enteric fever Lancet 2 806 1896

Although Widal s paper appeared first Grunbaum undoubtedly shares the credit for the development of this test as his work was carried on in Gruber s laboratory during the preceding year and was the direct outcome of Gruber and Durham s work on agglutination Grunbaum describes the microscopic method essentially as it is used today "It is only in cases of enteric fever that the serum shows a distinct agglutinative action within thirty minutes when diluted sixteen times and hence this reaction can be used as a diagnostic sign"

28 WRIGHT A E and SEMPLE D Remarks on vaccination against typhoid fever Brit. M J 1:256 1897

Wright and Semple s paper appeared shortly after that of Pfeiffer and Kolle They imply however that Pfeiffer plagiarized the idea from a paper of Wright s which appeared in the Lancet 21 807 (September 19) 1896 in which he claims to have put on record his first attempts at antityphoid inoculation An inspection of this paper makes the implication seem unfair to Pfeiffer since as the title would suggest (On the association of serous hemorrhages with conditions of defective blood coagulability") the observations concern themselves with other matters While it is mentioned incidentally that a horse and two men received injections of typhoid bacilli in connection with the experiments on blood coagulablity there is not the slightest suggestion that the writer contemplated purposeful antityphoid prophylaxis Pfeiffer s previous experimental work furthermore makes it evident that he already had the possibility of human immunization in mind

Wright and Semple used essentially the same procedure as Pfeiffer but they measured the result in terms of agglutinative titer of the serum of the subjects They found that such serum even if rich in agglutinins did not have any material bactericidal effect in vitro and hence they were more conservative than Pfeiffer in their conclusions as to the probable degree of protection which was to be expected Wright later described his results and those of others (Lancet, 2 651 1902)

29 MALLORY F B A histological study of typhoid fever J Exper Med 3 611 1898

Important studies of the finer histological changes

30 KEEN William W The surgical complications and sequels of typhoid fever Philadelphia W B Saunders 1898

A definitive monograph based on a careful analysis of reported cases and enriched by the author s wide experience It remains a storehouse of information on the (from the clinical standpoint) all important problem of typhoid complications

They used the term "paratyphoid" in the sense of "resembling typhoid" rather than in the strict modern technical sense The bacteriological distinction was made mainly on the basis of agglutination tests with specific sera

23 PFEIFFER R, and KOLLE W Ueber die specifische Immunitats reaction der Typhusbacillen, Ztschr f Hyg u Infectionskr 21 203 1895–96

The development of immunization was a logical sequel to preliminary studies Of these some of the most important were those of Pfeiffer and Kolle In a series of clean cut experiments they showed that the serum of typhoid con valescents contained substances which protected guinea pigs specifically against lethal doses of typhoid bacilli and that similar protective substances could be developed in the serum of goats following repeated injections of culture These observations together with practical results already obtained in cholera sug gested attempts at human prophylaxis

24 PFEIFFER R and KOLLE W Experimentelle Untersuchungen zur Frage de Schutzimpfung des Menschen gegen Typhus abdominalis Deutsche med Wchnschr 22 735 1896

Pfeiffer s attempts at prophylactic vaccination were stimulated by encouraging results which had been obtained in cholera Pfeiffer injected subcutaneously about 2 mg of fresh culture scraped from agar slants suspended in broth and sterilized at 56 C There was usually a chill within 2 or 3 hours followed by a rise in temperature to about 38 5 C Only one injection was given. Serum drawn from the subjects about 11 days after the treatment was found to have as high a titer of protective bodies against experimental guinea pig infection as did the serum of typhoid convalescents On this basis Pfeiffer hoped that the prophylaxis would convey as complete a protection as a spontaneous attack of typhoid fever since at that time the humoral bactericidal antibodies were re- garded as entirely or almost entirely responsible for recovery from the disease

25 GRUBER Max, and DURHAM Herbert E Eine neue Methode zur raschen Erkennung des Cholera vibrio und des Typhus Bacillus Mun chen med Wchnschr 4 285 1896

It was found that serum from guinea pigs immunized against cholera or typhoid developed the remarkable property when mixed with the bacteria in question under proper conditions of causing them to "stick together in large balls and to lose their motility We therefore have named these specific substances agglutinins " In discussing the implications of this finding, Gruber and Durham laid special stress on the identification of unknown strains of bacteria by known immune sera The alternative procedure of detecting specific immune bodies by testing against known cultures was however obvious and was later described from Gruber s laboratory by Grunbaum (see Ref 27)

26 WIDAL, F Sérodiagnostic de la fièvre typhoide Semaine méd 16 259 1896

While Widal s name has been attached to the agglutination test in typhoid the original communication seems brief and inadequate and gives no credit to Gruber and Durham who had already clearly described the phenomenon of

agglutination Widal added the patient s serum to broth cultures of typhoid bacilli in a proportion of 1 to 10 or 15 and incubated for 24 hours Gross floccu lation was observed at the end of this time

27 GRÜNBAUM Albert S Preliminary note on the use of the agglutinative action of human serum for the diagnosis of enteric fever Lancet 2 806 1896

Although Widal s paper appeared first Grunbaum undoubtedly shares the credit for the development of this test as his work was carried on in Gruber s laboratory during the preceding year and was the direct outcome of Gruber and Durham s work on agglutination Grunbaum describes the microscopic method essentially as it is used today "It is only in cases of enteric fever that the serum shows a distinct agglutinative action within thirty minutes when diluted sixteen times and hence this reaction can be used as a diagnostic sign"

28 WRIGHT A E and SEMPLE D Remarks on vaccination against typhoid fever Brit M J 1:256 1897

Wright and Semple s paper appeared shortly after that of Pfeiffer and Kolle They imply however that Pfeiffer plagiarized the idea from a paper of Wright s which appeared in the Lancet 21:807 (September 19) 1896 in which he claims to have put on record his first attempts at antityphoid inoculation An inspection of this paper makes the implication seem unfair to Pfeiffer since as the title would suggest (On the association of serous hemorrhages with con ditions of defective blood coagulability") the observations concern themselves with other matters While it is mentioned incidentally that a horse and two men received injections of typhoid bacilli in connection with the experiments on blood coagulablity there is not the slightest suggestion that the writer con templated purposeful antityphoid prophylaxis Pfeiffer s previous experimental work furthermore makes it evident that he already had the possibility of hu man immunization in mind

Wright and Semple used essentially the same procedure as Pfeiffer but they measured the result in terms of agglutinative titer of the serum of the subjects They found that such serum even if rich in agglutinins did not have any material bactericidal effect in vitro and hence they were more conservative than Pfeiffer in their conclusions as to the probable degree of protection which was to be expected Wright later described his results and those of others (Lancet, 2 651 1902)

29 MALLORY F B A histological study of typhoid fever J Exper Med. 3 611 1898

Important studies of the finer histological changes

30 KEEN William W The surgical complications and sequels of typhoid fever Philadelphia: W B Saunders 1898

A definitive monograph based on a careful analysis of reported cases and en riched by the author s wide experience It remains a storehouse of information on the (from the clinical standpoint) all important problem of typhoid com plications

31 CURSCHMANN H Der Unterleibstyphus Vienna Alfred Holder 1898

The most comprehensive modern clinical treatise with important literature to date arranged with the subject matter

32 KOCH, Robert Die Bekampfung der Typhus (Vortrag, gehalten in der Sitzung des wissenschaftlichen Senats bei der Kaiser Wilhelms Akademie am 28 November 1902) Veroffentlichungen aus dem Gebiete des Militar Sanitatswesens Vol 21 Berlin A Hirschwald 1903

The control of typhoid epidemics was the outstanding problem of the disease at the end of the nineteenth century While it was recognized that water and milk supplies contaminated by typhoid excreta were major factors it had not been clearly appreciated that the most adequate way to check the spread of the disease was by disinfection of excreta at their source and isolation of the convalescents until they became bacillus free In this famous lecture Koch clearly outlined the logical methods of typhoid control "There are therefore two conditions which must be fulfilled. In the first place we must be in a position to recognize the infectious agent with ease and certainty and in the second place to dispose of it To this end special methods of readily identifying the typhoid bacillus in the stools were developed (Von Drigalski and H Conradi "Ueber ein Verfahren zum Nachweis der Typhusbacillen" Ztschr f Hyg u Infectionskr 39 283 1902) and stations were set up in typhoid districts for the control of carriers These measures together with improvement in sewage conditions soon led to a great decrease in typhoid incidence in Germany

33 VON DRIGALSKI Ueber Ergebnisse bei der Bekampfung des Typhus nach Robert Koch, Centralbl f Bakt 35 776, 1904

Drigalski s work amplified and extended that of Koch (see Ref 32) especially with reference to carriers who had never had clinical typhoid fever Drigalski stressed the carrier as the main cause of continuous endemic typhoid in distinction to extensive outbreaks due to contaminated water He insisted on negative stool and urine cultures from convalescents before they were released from supervision

34 McCRAE T Typhoid fever *in* OSLER and McCRAE Modern medicine 2 70 Philadelphia and New York Lea Bros 1907 Also 3d ed 1 63 Philadelphia and New York Lea & Febiger 1925

The best modern English article based largely on the Johns Hopkins case

35 COLEMAN Warren Diet in typhoid fever J A M A 53 1145 1909

One of the most important contributions to the treatment of typhoid fever was the proof that a liberal diet could be taken with beneficial results While various clinicians from Robert Graves (1835) on had empirically advised the feeding of typhoid patients it remained for Coleman and his associates (see Refs 36 38 42) to establish by accurate scientific methods that food could actually be digested and absorbed and that nitrogen equilibrium could be maintained and weight loss prevented by high-calorie diets This was a radical departure from previous practice Until the high-calorie diet was introduced stress was placed

on intensive hydrotherapy (see E Brand, *Die Hydrotherapie des Typhus* [Stettin, 1861]) One of the most notable results of the liberal diet is shortening of the period of convalescence formerly so long and tedious This series of studies is of great importance not only in relation to typhoid but because the principles which were established apply to other prolonged fevers as well

36 SHAFFER Philip A and COLEMAN Warren Protein metabolism in typhoid fever Arch Int Med 4:538, 1909

In carefully controlled metabolism studies of typhoid patients it is shown that the destruction of body protein (and loss of weight) which had been ascribed not only to fever but to obscure "toxic effects" could be prevented by feeding 10-15 gm of nitrogen (60-90 gm of protein) daily together with an adequate carbohydrate ration W Coleman and E F DuBois showed later however ("Calorimetric observations on the metabolism of typhoid patients with and without food," Arch Int Med. 15:887 1915) that there was a "toxic" destruction of protein in typhoid, since patients might have a distinctly negative nitrogen balance on a diet which contained more than enough calories to cover heat production

37 SCHOTTMÜLLER, H Die Typhosen Erkrankheiten *in* MOHR and STAEHELIN Handbuch der inneren Medizin 1:371 Berlin Julius Springer 1911

Excellent summary with literature

38 DUBOIS Eugene F The absorption of food in typhoid fever Arch Int Med. 10 177 1912.

One of the principal arguments against liberal feeding in typhoid was disposed of by these experiments which showed that protein and carbohydrate could be absorbed as well as during health and that the absorption of fat was only moderately diminished

39 LEDINGHAM J C G and ARKWRIGHT J A The carrier problem in infectious diseases New York Longmans Green & Co 1912

An authoritative summary of the carrier problem

40 KUTSCHER K H Abdominal typhus *in* KOLLE and WASSERMANN Handbuch der pathogenen Micro-organismen 3:717 2d ed. Jena Gustav Fischer 1913

Comprehensive review of the bacteriology of typhoid

41 FORNET W Immunitat bei Typhus *in* KOLLE and WASSERMANN Handbuch der pathogenen Micro-organismen, 3 837 2d ed Jena Gustav Fischer 1913

Comprehensive review of immunological aspects of typhoid fever

42 COLEMAN Warren The influence of the high calorie diet on the course of typhoid fever J A.M A 69 329 1917

A summary of the end results of the treatment

43 GAY, F P Typhoid fever New York Macmillan Co 1918

A comprehensive summary of knowledge of the disease from the biological and epidemiological standpoint The Bibliography is especially well selected and complete

44 CHRISTELLER E Der Typhus abdominalis *in* HENKE and LUBARSCH Handbuch der speciellen pathologischen Anatomie und Histologie 4 500 Berlin Julius Springer 1924

Special emphasis on pathological changes Extensive bibliography Good colored plates of lesions gross and histological

45 WOODWARD, T E SMADEL J E, LEY H L Jr GREEN R and MANKIKAR D S Preliminary report on the beneficial effect of chloromycetin in the treatment of typhoid fever Ann Int Med 29 131 1948

For nearly one hundred years typhoid fever remained refractory to every available drug, and the mortality was essentially unchanged Woodward and his associates were engaged in testing a new antibiotic, chloromycetin (*J Ehrlich Q R Bartz R M Smith, D A Joslyn and P R. Burkholder Chloromycetin* a new antibiotic from a soil actinomycete," Science 106 417 1947) in cases of scrub typhus in Malaya when it occurred to them to use the drug in the severe cases of typhoid fever which were present in the area Ten cases were treated Fever as a rule dropped rapidly and the patients felt much better in a few days Blood cultures promptly became sterile Two of the ten patients (20 per cent) developed relapses with bacteremia after afebrile periods of 10 and 16 days In one case intestinal perforation occurred on the second day of normal temperature and in another a large intestinal bleeding took place on the fourth day of normal temperature Woodward (Chloromycetin and aureomycin therapeutic results" Ann Int Med 31 53 1949) soon reported further experiences Woodward Smadel and Ley (Chloroamphenicol and other antibiotics in the treatment of typhoid fever and typhoid carriers" J Clin Investigation 29 87 1950) analyzed the treatment of 24 patients with chloramphenicol without a death Again the relapse rate was about 20 per cent The drug also failed to eliminate typhoid bacilli permanently from chronic carriers

Meanwhile Vernon Knight and his associates (*V Knight, F Ruiz Sanchez* A Ruiz Sanchez, S Schultz, and W McDermott, "Antimicrobial therapy in typhoid" Arch Int Med 85:44 1950) working with the severe typhoid fevers of Mexico reported 13 cases treated with chloramphenicol without a death J E Smadel C A Bailey and R Lewthwaite ("Synthetic and fermentation type chloramphenicol [chloromycetin] in typhoid fever prevention of relapses by adequate treatment" Ann Int Med 33 1 1950) alive to the frequency of relapses prolonged the use of the drug to 14 days which they found adequate to prevent relapse in their series

Thus typhoid fever at long last has been to a large extent mastered by medical science

Section 2

CHOLERA

Anticholera vaccination	Ref 16
Bacteriology	Refs 11 12 17 22 24
Carriers	Ref 21
Clinical	*Refs 1 4*
Epidemiology	Refs 2, 7 8 9 10 14
General	Refs 1 2 4 5
Immunity	Refs 12, 13 15
Pathology	Refs 5 6 20
Serum therapy	Ref 18
Treatment, antibiotic	Ref 23
Treatment with salts and fluids	Refs 3 19

Section 2

CHOLERA

WE HAVE found no really comprehensive modern bibliography of cholera Much of the early literature deals with descriptions of outbreaks of epidemics and this phase of the subject is comprehensively dealt with by Hirsch (Ref 10) as well as by C Macnamara in *A History of Asiatic Cholera* (London Macmillan & Co 1876) A good general account of the disease is that of H Harold Scott in his *History of Tropical Medicine* (Baltimore Williams & Wilkins Co 1939) 2 694 C Liebermeister s *Cholera Asiatica und Cholera Nostras* (Vienna Alfred Holder 1896) has appended to it a fairly comprehensive bibliography of the older literature Finally J S Chambers in his book *The Conquest of Cholera* (New York Macmillan Co 1938) gives in interesting detail the story of cholera especially in the United States

1 BRIGHAM A Treatise on epidemic cholera including an historical account of its origin and progress to the present period Hartford Conn H & F J Huntington 1832

Although epidemics of what was pretty clearly cholera had been described at various times (Ref 10) the modern history of the disease dates from the out break at Jessore in India in 1817 Brigham s book opens with a year by year description of the progress of this epidemic which spread over India during the ensuing years but did not reach Asia Minor and China until 1823 In 1829 the disease crossed the Urals and in 1830 spread along the Volga reaching Moscow In 1831 it appeared in many parts of Europe including Berlin In this year it also reached England (for detailed accounts of the various epi demics see Ref 10) Next come accounts of the disease from various parts of the world In the cases seen by the writer in New York he describes the symptoms as follows "First, diarrhoea though often of only short duration then nausea and vomiting though in some instances the vomiting was slight to which succeeded a sinking of the circulation coldness and blueness of surface burning thirst spasms and death In most of the cases that I have seen the discharges from the stomach and bowels were light colored, resembling arrow root and water or starch and water and were without odor" (p 104) In another account (p 102) the stools are described as being "like rice water" "Besides the intestinal canal and skin all other organs furnished no secretion Tears pituita saliva and urine the secretion of which is totally suspended as to tears the greatest anguish of dying in full possession of the intellect, surrounded by all that is at once endearing and afflicting could not produce them" The thickness of the blood is remarked and it is stated that leeches could procure none "The accounts of this disease from Asia Persia Russia Poland England Canada and the United States all agree" (p 105) The descriptions of "Appearances on Dissection" follow aside from the evidence of desiccation there is disagreement as to the significance of the findings In some cases the gastrointestinal tract is said to show little in others there were extensive lesions of the superficial layers

As to treatment it is hard to see how physicians could have failed to note

the obvious evidences of dehydration instead bleeding and leeching and the usual variety of meaningless drugs were advised In one account (p 163) it is stated "Let two tablespoons full of common kitchen salt dissolved in six ounces of warm water be given immediately" That the writer had no rational basis for this prescription becomes clear when he adds "energetic complete vomiting will probably be produced by the salt" However he adds later (p 176) "The patients treated in this manner that is with a solution of common salt, were often very soon restored to health, and could hardly be recognized after a few hours" On page 243 however a most interesting statement appears "A few have been cured in New York by the injection of saline solutions into the veins Dr Rhinelander stated to the Board of Health of New York the case of Margaret Mehan who was cured at Crosby Street hospital by injecting into the veins twenty four ounces of a solution composed of one dram of carb soda and two drams of muriate of soda [common salt] dissolved in six pints of water The operation was performed at 7 P M on July 21st [1832?] Several other cases of cholera have been cured in a similar manner both in this country and also in England where the practice I believe originated This practice is undoubtedly founded upon the fact said to have been discovered by analysis that the blood drawn from a patient affected with cholera has lost a portion of its watery and albuminous parts and also most of its natural saline ingredients"

There are introduced at this point two lectures by J F V Broussais of which the most interesting part is the discussion of contagion The fact that several members of a household often had the disease "gives rise to the suspicion that there is a species of infection by which the patient communicates the disease to those who have charge of him" But, by their number and vociferousness the anticontagionists vastly predominated at this time

2 BELL, G H Treatise on cholera asphyxia or epidemic cholera 2d ed Edinburgh William Blackwood, 1832

Cholera went under a variety of descriptions cholera asphyxia blue cholera epidemic cholera Asiatic cholera cholera morbus etc many used the term "cholera morbus" for sporadic cases in distinction to the epidemic. This book, like many others at the time deals with the whole subject. Worthy of mention however is the discussion on contagion "Much stress has been laid on the fact that the Cholera has travelled along the banks of rivers Undoubtedly it has done so but in so far as regards India the writers who rely so confidently on this fact have not adverted to the peculiarity that the progress of the disease along the banks of rivers has not been confined, as they seem to suppose to navigable rivers It has extended itself along the banks of rivers whether navigable or not" (p 84) No one sensed the fact that the disease might be conveyed by contamination of the river water

3 Documents communicated by the Central Board of Health London relative to the treatment of cholera by the copious injection of aqueous and saline fluids into the veins Lancet 2:274 1832

The first approach to a rational therapy for cholera was by W B O Shaughnessy ("Proposal of a new method of treating the blue cholera epidemic by the injection of highly-oxygenated salts into the venous system" Lancet 1:366

1831-32) who was impressed by the thick black blood and recognized the *need of restoring it to an oxygenated or arterial state* This he proposed to do by injection into the vein of "oxygenated salts" such as potassium nitrate and potassium chlorate Nothing came of this, but a little later ("Experiments on the blood in cholera" Lancet, 1 490, 1831-32) O Shaughnessy reported analyses of blood from cholera patients which gave him a lead in the right direction He found the blood "has lost a large proportion of its water it has lost also a great proportion of its *neutral* saline ingredients" and that "of the free alkali contained in healthy serum, not a particle is present" He also found that "urea exists in the cases where suppression of urine has been a marked symptom" and that all the salts deficient in the blood especially the carbonate of soda are present in large quantities in the peculiar white dejected matters" O Shaughnessy issued a larger report on these findings with therapeutic suggestions which was reviewed in critical if not hostile fashion later in the year ("Report on the chemical pathology of the malignant cholera" (review) Lancet 1 929 1831-32) He says "When absorption is entirely suspended as in those desperate cases which are unhappily now of daily occurrence in this metropolis the author recommends the injection into the veins of tepid water holding a solution of normal salts of the blood" Meanwhile W Reid Clanny ("Case of cholera at Sunderland with an analysis of the blood taken from the patient" Lancet 1 505 1831-32) found that "in Elliot Todd [the patient] water colouring matter and muriates of soda and potassa and carbonate of soda were respectively 644 253 and 0 parts as against the findings in The Sailor [control] 756 59 and 14 parts" The matter was soon pressed further (W B O Shaughnessy "Chemical pathology of cholera" Lancet 2 225 1831-32 Clanny "Composition of healthy and cholera blood" Lancet 2 232 1831-32) However the first practical application of the method seems to have been made by Thomas Latta as reported in the above mentioned "Documents" Latta was stimulated by reading *O Shaughnessy s report on the blood in cholera* "The first subject of experiment was an aged female She had apparently reached the last moments of her earthly existence and now nothing could injure her Having inserted a tube in the basilic vein cautiously—anxiously I watched the effects ounce after ounce was injected, but no visible change was produced Still persevering, I thought she began to breathe less laboriously soon the sharpened features and sunken eyes and fallen jaw pale and cold bearing the manifest imprint of death s signet, began to glow with returning animation the pulse which had long ceased returned to the wrist and in the short space of half an hour when six pints had been injected she expressed in a firm voice that she was free of all uneasiness actually became jocular and fancied all she needed was a little sleep her extremities were warm and every feature bore the aspect of comfort and health" The patient soon became worse again and died no further salt solution was injected

Latta later worked out a formula—2 or 3 drams of muriate of soda and two scruples of the subcarbonate in 6 pints of water injected at temperature of 112 F He believed that larger amounts must often be given and attributed failure mainly to "too little and too late" A moribund woman was restored by injection of 330 ounces (9 900 cc.) "in 48 hours she smoked her pipe free from distemper" and proceeded to get well. "The apparatus I have used is Read s patent syringe having a small silver tube attached to the extremity of the flex

ible injecting tube The syringe must be quite perfect so as to avoid the risk of injecting air"

The report continues with abstracts of cases in which the saline therapy was used by Drs Lewin Craigie Macintosh and Racy All agreed on the undoubted benefits of this form of treatment We learn incidentally of the impunity with which unsterile solutions may be injected into the vein

During the ensuing year there are more case reports in the Lancet some favorable some unfavorable but with the subsidence of the epidemic this mode of therapy seems to have been neglected although scattered case reports and notes are found through the years The procedure never became standard ized and as late as 1873 A Netter ("Des injections qui se pratiquent dans les veines des cholériques et de la causes des variations des résultats obtenus jusqu ici avec ce moyen thérapeutique" Gaz. hôp Paris 46:1107 1873) ana lyzes the difficulties and uncertainties of the method pointing out that while the immediate results are almost uniformly promising the later effects are vari able He analyzed the situation more at length in a little monograph (A Netter *Vues nouvelles sur le choléra avec une étude sur les injections faites dans les veines* [Paris J B Baillière et fils 1874]) The whole subject was later re viewed by Rogers (Ref 19)

4 History of the rise progress ravages etc. of the blue cholera of India (editorial) Lancet 1:241 1831–32

With the recent outbreak of cholera in England, the weekly medical journals for 1831–32 are filled with notes suggestions and case reports of the disease The present article of 43 pages gives an authoritative review of current knowl edge After a section on the origin and spread of epidemic cholera there is a vivid description of the symptomatology emphasizing the vomiting and purging followed by muscle cramps anuria pulselessness and the bluish shrunken appearance of the skin As to pathology emphasis is placed on the huge quan tity of turbid fluid in the bowel with the deposit of immense amounts of "an argilaceous substance" Changes in the mucous membrane are also mentioned "Every character of the cholera authorizes us in concluding that it arises from failure of a portion of the *nervous system* [Bell]" The writers did, however feel that cholera was communicable and quote the conclusions of Drs Russell and Barry "1 That the poison of cholera may be conveyed and communicated by man to man. 2. That like the poison of typhus it is regenerated in great quantities by those who suffer its influence" The arguments against contagion are next summarized, and then there is a discussion of the confused irrational ideas on treatment which existed at the time[1] It is of interest to read the argu ments whereby almost everyone agreed on bleeding as the backbone of therapy

[1] "The whole of Europe is little more than a vast advertisement, in which are an nounced, in colossal letters the admirable recipes for the preservation against and the cure for this disorder Here cincture is advised there an elixer is lauded and every where we meet abundant proof that if this is the age of intelligence knavery is not less on the increase But even among men of the utmost science and purest intentions equal diversity of sentiment prevails One advocates venesection while another as energetically cries it down Sedatives and stimulants emetics cathartics and specifics each have their strenuous supporters It is worthy of remembrance too that these dis cussions are the fiercest among the actual witnesses of the disease"

The article concludes with a *discussion of sanitary measures* especially the quarantining of ships There is no mention of contaminated water playing a part in contagion

5 TARDIEU A Du choléra épidémique Paris Germer Baillière 1849

These interesting lectures make clear that there had been no advance in under standing of the disease since the studies made in the epidemic of 1832 The usual atmospheric and telluric causes are discussed and as to the contagion "we have seen the most ingenious theories the most appealing even for keen minds fall before an examination of the facts" (p 148) As to treatment there are mentioned ipecac Dover s powder calomel bismuth subnitrate cubebs ammonia camphor ether oil of Cajeput guaco hashish chloroform as well as "the barbarous attempts at transfusion of blood or injection of water into the veins" One can see that intravenous therapy was making no progress

The clinical descriptions are vivid, and there is an excellent section as one might expect from the French on the pathology of cholera

6 Report of the [Boston] Committee of Internal Health on the Asiatic chol era Boston I H Eastburn 1849

This careful report was issued as a result of the Boston epidemic of cholera in 1849 The major part of the book consists of detailed autopsy reports of 33 cases No general conclusions are drawn but in most of the cases the fluid *material in the bowel* and the *changes in mucous membranes are stressed* "Examined by the microscope [the bowel contents] the flocculi suspended in the rice water fluid invariably consisted of columnar epithelium The epithe lium cells were so abundant and well-defined as to leave no doubt that they constituted nineteen twentieths of the mass of the flocculi If maceration how ever *is the only cause of the separation of such an enormous quantity of* epithelium how shall we explain it in the situations where no increased amount of fluid has existed? The mucous surfaces of the vagina and of the urinary bladder are invariably smeared with a thick whitish pasty or creamy secretion which on microscopic examination is seen to consist entirely of detached epithe *lium cells*" (p 47) *Under "Treatment" it is stated that narcotics "totally failed* of any beneficial effect" The same was true of stimulants emetics calomel, quinia, tannic acid, ginger cinnamon and elaterium Ether by inhalation re lieved the cramps but no one recovered who used it in this way As to venous injection "*In one or two cases there was temporary relief but death invariably followed shortly after We were not inclined to make new trials of this mode* of treatment after the first six weeks of the epidemic" The time was not yet ripe to use the method properly

7 SNOW J On the mode of communication of cholera London J Churchill 1849

Snow advanced the view that cholera was disseminated by something in the fecal discharges of patients which was later ingested by healthy people who thus acquired the disease He stressed contaminated water supplies *as the chief* source This was not a "study-chair" piece of reasoning but Snow was inde fatigable in field work which seemed to support his views However he could not at first gain any attention In the monumental *Report of Epidemic Cholera Drawn up at the Desire of the Cholera Committee of the Royal College of*

Surgeons by William Baly and William W Gull (London John Churchill 1854) for example six theories of causation are mentioned as possibilities "The *Third* theory—that propounded by Dr Snow—gives a more specific form to the doctrine of contagion It supposes that the poison of cholera is swallowed and acts directly on the mucous membrane of the intestines is at the same time reproduced in the intestinal canal and passes out much in creased with the discharges and that these discharges afterwards in various ways but chiefly by becoming mixed with the drinking water in rivers or wells reach the alimentary canals of other persons and produce the like disease in them" (p 5) But after several hundred pages of analysis the experts reject Snow's views "Of the six theories then that alone is supported by a large amount of evidence which regards the cause of Cholera as a matter increasing by some process whether chemical or organic in impure or damp air and assumes that although, of course diffused with the air it is also distributed and diffused by means of human intercourse" (p 223) But Snow fought on and on January 21 1854 for example he spoke at the Medical Society of London as reported in the Lancet (1:109 1854) There he laid out a rational method of therapy emphasizing "medicines which have the effect of destroying low forms of organized beings" to be given for their local effect and that "it was useless to attempt to bring the patient out of the state of collapse by stimulants and the application of heat and they should be given watery drinks unless in desperate cases in which it might be desirable to inject into the blood vessels a weak saline solution resembling that portion of the blood which has been lost." The reporter continues "Indeed, if a layman had been present at the meeting, he might have witnessed a remarkable illustration in the way in which doctors differ and surely his faith in physic would have been scarcely in creased in strength Every speaker seemed to have an opinion of his own on the subject of the nature and cause of the disease The treatment was no less contradictory" Snow continued however to collect evidence in support of his views and in 1855 published a "Second Edition much Enlarged of his book, which embodies the contents of numerous papers published in the contem porary medical journals This second edition has been reproduced as a belated tribute to Dr Snow in facsimile (*Snow on Cholera Being a Reprint of Two Papers by John Snow M D* [New York Commonwealth Fund 1936]) Snow did for cholera what Budd did for typhoid fever and his work is required reading for all interested in the subject

8 PETTENKOFFER M Untersuchungen und Beobachtungen uber die Verbreitungsart der Cholera nebst Betrachtungen über Massregeln dersel ben ein Halt zu thun Munich J G Cotta 1855

This book, the work of Pettenkoffer the famous hygienist is based on meticu lous observations on the cholera outbreak in Bavaria in 1854–55 Pettenkoffer's work consisted of careful study of the details of the epidemic and is definitely modern in tone By studying spot maps of the location of cases in Munich and elsewhere he convinced himself that contaminated water had nothing to do with the spread of cholera He was sure, however that the disease was com municable he believed that the agent was present in urine and stools and he consequently developed an elaborate system of disinfection By 1875 Pet tenkoffer had not changed his views a great deal (*Kunftige Prophylaxis gegen Cholera besprochen von Max v Pettenkoffer* [Munich Th Riedel 1875]) He

The article concludes with a discussion of sanitary measures especially the quarantining of ships There is no mention of contaminated water playing a part in contagion

5 TARDIEU, A Du choléra épidémique Paris Germer Baillière 1849

These interesting lectures make clear that there had been no advance in under standing of the disease since the studies made in the epidemic of 1832 The usual atmospheric and telluric causes are discussed and as to the contagion "we have seen the most ingenious theories the most appealing even for keen minds fall before an examination of the facts" (p 148) As to treatment there are mentioned ipecac Dovers powder calomel bismuth subnitrate cubebs ammonia camphor ether oil of Cajeput guaco hashish chloroform as well as "the barbarous attempts at transfusion of blood or injection of water into the veins" One can see that intravenous therapy was making no progress

The clinical descriptions are vivid, and there is an excellent section as one might expect from the French on the pathology of cholera

6 Report of the [Boston] Committee of Internal Health on the Asiatic chol era Boston I H Eastburn 1849

This careful report was issued as a result of the Boston epidemic of cholera in 1849 The major part of the book consists of detailed autopsy reports of 33 cases No general conclusions are drawn but in most of the cases the fluid material in the bowel and the changes in mucous membranes are stressed "Examined by the microscope [the bowel contents] the flocculi suspended in the rice water fluid invariably consisted of columnar epithelium The epithe lium cells were so abundant and well-defined as to leave no doubt that they constituted nineteen twentieths of the mass of the flocculi If maceration how ever is the only cause of the separation of such an enormous quantity of epithelium how shall we explain it in the situations where no increased amount of fluid has existed? The mucous surfaces of the vagina and of the urinary bladder are invariably smeared with a thick whitish pasty or creamy secretion which on microscopic examination is seen to consist entirely of detached epithe lium cells" (p 47) Under Treatment" it is stated that narcotics "totally failed of any beneficial effect The same was true of stimulants emetics calomel, quinia tannic acid ginger cinnamon and elaterium Ether by inhalation re lieved the cramps but no one recovered who used it in this way As to venous injection "In one or two cases there was temporary relief but death invariably followed shortly after We were not inclined to make new trials of this mode of treatment after the first six weeks of the epidemic" The time was not yet ripe to use the method properly

7 SNOW J On the mode of communication of cholera London J Church ill 1849

Snow advanced the view that cholera was disseminated by something in the fecal discharges of patients which was later ingested by healthy people who thus acquired the disease He stressed contaminated water supplies as the chief source This was not a "study-chair" piece of reasoning but Snow was inde fatigable in field work which seemed to support his views However he could not at first gain any attention In the monumental *Report of Epidemic Cholera Drawn up at the Desire of the Cholera Committee of the Royal College of*

tion to date Various epidemics all over the world are listed and documented For more recent lists of outbreaks see Carl Mense *Handbuch der Tropenkrankheiten* (2d ed Leipzig Barth 1914) 3:213 ff H Harold Scott *A History of Tropical Medicine* (Baltimore Williams & Wilkins Co 1939) 2:663 ff and Sir Leonard Rogers *Bowel Disease in the Tropics* (London Henry Frowde 1921) chap 1 pp 1 ff C. Macnamara s *A History of Asiatic Cholera* (London Macmillan & Co 1876) may also be consulted

II Conferenz zur Erorterung der Cholerafrage Verhandelt Berlin im Reichsgesundheitsamt am 26 Juli 1884 Abends 6 Uhr Berl Klin Wchnschr 21:477 493 1884 (English translation of Koch s remarks Brit. M J 2:403 453 1884)

Koch tells how he went to Egypt to study cholera After doing many autopsies he convinced himself that the only plausible place to seek the germ was in the intestines The changes varied from very slight lesions to reddening and swelling of Peyer s patches or even to a necrosis of the mucosa with a diphtheritic covering On sections it was found that the space between the epithelium and *the basement membrane of the glands was crowded with numerous comma* shaped bacilli These were also found in the intestinal contents The organisms and their cultural characteristics are described in detail Koch found that the organism was short lived and did not survive when dried on clothes or in soil He found the comma bacillus in the dejecta of numerous cholera cases in almost pure culture "In accordance with the cholera material that I have so far examined I think I can now assert that comma bacilli are never found absent in cases of cholera they are something that is specific to cholera " In patients with other diseases the comma bacilli were never found, nor were they obtained from two men who had had cholera respectively six weeks and eight days previously Koch recognized however that further proof of the causal role of the bacillus was necessary and he fed numerous small animals with fresh dejecta and with cultures All remained well He observed however that several laundresses who handled cholera linen came down with the disease this he accepted as strong evidence "If therefore an infection can be brought about by cholera linen then as the comma bacilli are the only micro-organisms in question it can only be brought about by them " He asked how an organism confined to the intestine can make a person so ill and suggested that the germs produce soluble absorbable toxins He recovered comma bacilli from a large tank in which a number of people did their washing and from which they also drank the water He thought water and moist food the commonest ways of infection dried material was a less likely source Koch pointed out that the same person was rarely affected twice in the same epidemic he concluded therefore that the disease was followed by a temporary immunity Finally he hoped that the discovery of the cholera bacillus would be of use in diagnosis and therapy

The article like Koch s work on the tubercle bacillus seems complete and unassailable it should be carefully studied by all interested in the subject

In another paper ("I Uber die Cholerabacterien " Deutsche med Wchnschr 10 725 1884) Koch discussed the subject further and answered certain objections made by others He did not mention dehydration and salt loss as a feature of this disease

Koch went to India and confirmed the results he had obtained in Egypt

believed that there was a specific cholera germ which occurred principally in the stools but that its transmission was bound up with certain special conditions of the soil and ground water He still laid stress on disinfection of stools and everything else the cholera patient came in contact with

9 FAUVEL A Le choléra étiologie et prophylaxie etc exposé des travaux de la Conférence Sanitaire Internationale de Constantinople Paris J B Baillière et fils 1868

By the time of the epidemic of 1865–66 opinion had swung strongly to the view that cholera was contagious As to the nature of the "materies morbi" and the mode of its propagation there was however great dispute Innumerable books and articles were published of which we may mention as examples that of Bernard M Byrne (*An Essay To Prove the Contagious Character of the Malignant Cholera* [2d ed Philadelphia Childs & Peterson 1855]) as well as *A Communication from the City Physician on the Asiatic Cholera Is It a Contagious Disease?* (City of Boston City Doc No 21] [1866]) Of great importance however is the Report to the International Sanitary Conference* This body consisting of 21 physicians representing various nations was sent by the French government to Egypt at the start of the epidemic of 1865 "to study the progress of the disease its march and its special character with a view to arresting its onward movement" This valuable document of some 100 pages takes up the subject of cholera as a series of 33 questions which are discussed analyzed and voted on by the members of the commission for acceptance or rejection The commission accepted unanimously the proposition that cholera is propagated by man and is transmissible They concluded however that the principal mode of transmission was by emanation into the air although water and certain ingesta might also serve as vehicles for the introduction into the organism of the generative principle of cholera through the respiratory passages and very probably also the digestive canal The germ however was mainly in the dejecta and took its origin probably in the digestive canal They thought that the "germ could be transmitted only during the first few days of the disease Many other questions are discussed This document is especially important as representing the carefully considered views of a large group of top flight physicians and scientists An abstract of the report appeared in the Boston Medical and Surgical Journal ("Report of the cholera conference at Constantinople 75 42 1866) and an English translation of part of the full report appeared in Boston in 1867 *

10 HIRSCH A Handbuch der historisch geographischen Pathologie Indische Cholera 1 279 2d ed Stuttgart Ferdinand Enke 1881 (HIRSCH A Handbook of Geographical and Historical Pathology English translation by Charles Creighton M D 1 394 London New Sydenham Society 1883)

Much of the literature on cholera is concerned with the epidemiology and with descriptions of outbreaks Hirsch s book is the classical storehouse of informa

* *Report to the International Sanitary Conference of a Commission from That Body to Which Were Referred the Questions Relative to the Origin Endemicity Transmissibility and Propagation of Asiatic Cholera* translated by Samuel L Abbot M D (Boston Alfred Mudge & Son 1867)

15 PFEIFFER R and ISSAEFF Über die specifische Bedeutung der Choleraimmunität Ztschr f Hyg u Infectionskr 17:355 1894

This is the classical paper in which was described what was later known in immunology as the Pfeiffer phenomenon" The authors showed that cholera vibrios injected into the peritoneum of an immune guinea pig underwent rapid dissolution if another organism was injected or if the guinea pig was non immune the injected bacteria were unaffected Pfeiffer therefore made an important contribution to the knowledge of cholera and discovered a general immunological principle as well The protection turned out to be purely anti bacterial as the animals were just as sensitive to cholera "toxin" Pfeiffer later ("Weitere Untersuchungen uber Wesen der Choleraimmunitat und uber spe cifisch bactericide Processe" Ztschr f Hyg u Infectionskr 18 1 1894) re-stated his principle that "serum of animals which are actively immunized against cholera only shows a specific action against the vibrios whereas against other bacteria it behaves no differently than the serum of normal animals" In this elaborate paper he gave the details of further studies with vibrios and toxin" in rabbits and guinea pigs Pfeiffer assumed that his reaction could *take place only in the animal body* but Metchnikoff (E Metchnikoff "Études sur l immunité sixième mémoire Sur la destruction extracellulaire des bac téres dans organisme" Ann Inst Pasteur 9:369 1895) soon demonstrated extracellular lysis in hanging-drop preparations

16 HAFFKINE W M Anti-cholera inoculation report to the Government of India Calcutta Thacker & Spink, 1895 See also HAFFKINE W M Protective inoculation against cholera London W Thacker & Co 1913

Ferrán in 1885 (J Ferrán "Nota sobre una vacuna quinca contra el cólera asiático" Rec cien méd Barcelona 11:515 1885) was apparently the first worker who claimed to produce immunity against cholera by subcutaneous injection of cholera bacilli In another note ("Sur la prophylaxie du choléra au moyen d injections hypodermiques de cultures pures du bacille-virgule Compt rend Acad d sc. 101 147 1885) Ferrán described his method which con sisted simply of subcutaneous injections at 5-day intervals of three doses of a living broth culture of the bacilli "I affirm to the Academy that the manner of abruptly interrupting the curve of mortality of an epidemic of cholera has today been accomplished by science" Ferrán did not however give any actual protocols and his work seems to have been questioned at the time A little later W M Haffkine ("Le Choléra asiatique chez le cobaye" Compt rend Soc de biol 44 635 1892) succeeded with injections of attenuated live chol era bacilli in rendering guinea pigs immune "An animal having been vacci nated first with attenuated and then with exalted virus is protected against *every infection with cholera no matter how one tries to produce it*" He soon (Le Choléra asiatique chez le lapin et chez le pigeon, *ibid* p 671) reported the same findings with rabbits and finally he showed that man could be safely injected with living cholera bacilli ("Inoculations de vaccines anticholériques à l'homme *ibid* p 740) E H Hankin ("Remarks on Haffkine s method of protective inoculation against cholera Brit M J 2 569 1892) submitted himself to inoculation by Haffkine and describes his own febrile and local reactions "The evidence shows that M Haffkine s method of inoculation is not attended by any grave disturbance of health and that it can be practiced on

As with every important bacteriological discovery there were some who doubted and some who obtained contradictory results In another communica tion ("Further researches on cholera Brit M J 1 6 1886) Koch systemati cally answered (and demolished) his opponents He also discussed animal experiments and he thought that he had produced cholera in guinea pigs

12 PFEIFFER R Untersuchungen uber das Choleragift, Ztschr f Hyg u Infectionskr 11 393 1892

The cholera bacillus was discovered during the lush flourishing of the bacterio logical era Everyone looked to immunological methods of diagnosis protection and therapy There was an immediate debate as to whether cholera bacilli re mained in the intestine and secreted a soluble exotoxin or whether in process of disintegration they yielded poisonous endotoxin Pfeiffer made pioneer ex periments to try to answer this problem he injected small animals with broth cultures with bacteria free filtrates and with living and dead bacteria "In young aerobic cholera cultures there is a specific poison which displays extraor dinary intense toxic action This primary cholera poison is very closely re lated to the bacterial bodies and is perhaps an integral part of them Pfeiffer later ("Studien zur Choleraatiologie" Ztschr f Hyg u Infectionskr 16 268 1894) elaborated these ideas He produced immune sera of which "very small amounts are adequate to confer on guinea pigs pronounced protection against intraperitoneal injection of cholera virus" Issaeff ("Untersuchungen uber die kunstliche Immunitat gegen Cholera" Ztschr f Hyg u Infectionskr 16 287 1894) confirmed Pfeiffer s work and showed that serum of human convalescents from cholera had high protective qualities against the bacteria but not against the endotoxins of the vibrios

13 WASSERMANN A Untersuchungen uber Immunitat gegen Cholera asiatica Ztschr f Hyg u Infectionskr 14 35 1893

Although empirical attempts at human immunization against cholera had al ready been made by Ferrán (Ref 16) it remained for the German workers to lay the experimental background In the present paper the writer showed that it is definitely possible to protect guinea pigs against the intraperitoneal infection with living cholera bacilli In order to achieve this one must inject cholera vibrios or their body substance in such doses that a mild specific illness a general reaction follows" R Pfeiffer and A Wassermann (Untersuchungen uber das Wesen der Choleraimmunitat" Ztschr f Hyg u Infectionskr 14 46 1893) continued this work and emphasized the need of a clear experimental foundation before human beings were treated

14 KOCH R Wasserfiltration und Cholera Ztschr f Hyg u Infectionskr *14 393 1893*

In 1892 occurred the famous cholera epidemic affecting especially Hamburg which was supplied with unfiltered water from the River Elbe whereas the adjacent cities of Altona and Wandsbeck which differed only in having a fil tered water supply had practically no cases of the disease Koch discusses this situation in detail and draws the inevitable conclusions as to the epidemiology of cholera Koch pursues the matter further (Die Cholera in Deutschland wahrend des Winters 1892 bis 1893" Ztschr f Hyg u Infectionskr 15 89 1893) in a long and interesting article

17 GOTSCHLICH F Über Cholera und choleraähnliche Vibrionen unter den aus Mekka zurückkehrenden Pilgern Ztschr f Hyg u Infectionskr 53:281 1906

Sooner or later it was inevitable that vibrios resembling those specific for cholera would be found Gotschlich working at the quarantine station at El Tor examined the intestinal content of 107 pilgrims dead of various forms of dysentery or colitis but not of cholera in which he found vibrios in 38 cases Many of these strains were agglutinated in high titer in anticholera sera but they were actively hemolytic and differed in certain other respects from true cholera vibrios The problem is fully discussed by Linton (Ref 22) At any rate it is established that vibrios resembling those of cholera but harmless or causing other bowel disturbances exist not infrequently

18 KOLLE W Zur Frage der Serumtherapie der Cholera asiatica Deutsche med Wchnschr 35: 2046 1909

Since serum therapy has in the end been abandoned in cholera we shall not attempt any lengthy bibliography However serum therapy had an active vogue at the turn of the century and so it should not be entirely ignored Kolle s paper is a summary of the whole situation by an authority in the field He points out that the great difficulty is that cholera patients die of "intoxication" and not of bacterial invasion whereas immune serum is essentially antibacterial He reports a death rate of 37 5 per cent in serum treated cases of severe cholera and in general is conservative in his predictions of the future of cholera immunotherapy

19 ROGERS L The treatment of cholera by injections of hypertonic saline solutions with a simple and rapid method of intraabdominal administration Philippine J Sc 4:99 1909

We have already reviewed the early efforts at intravenous saline therapy in cholera (Ref 3) Even in modern times it was variously judged Rogers (*Recent Advances in Tropical Medicine* [2d ed Philadelphia P Blakiston s Sons 1929] p 192) cites death rates of from 59 to 70 per cent Henry J Nichols and Vernon L Andrews ("The treatment of Asiatic cholera during the recent epidemic," Philippine J Sc 4 81 1909) on the other hand felt that they had reduced the death rate to 20–40 per cent by intravenous infusions of 0 85 per cent salt solution Rogers however not having had good final results with isotonic saline concluded that salt was lost out of proportion to fluid and therefore doubled the strength of his solution "On rapidly increasing the strength to double that formerly used (2 drachms of sodium chloride to the pint or 1 35 per cent to which 3 grams of calcium chloride may be added) a most gratifying degree of success was obtained "

The mortality was reduced from 61 to 32 5 per cent He calculated the amount of solution to be given by estimating the percentages of serum and corpuscles with the haemocrite " Rogers later ("A simple curative treatment of cholera " Brit M J 2 835 1910) discussed the treatment further and added to the saline injections internal administration of potassium permanganate to destroy "the specific toxins within the alimentary tract " He felt that he had increased the recovery rate seven fold The idea of using salt solution more concentrated than isotonic saline was not however new when Rogers applied it

human beings with perfect safety A little later A E Wright and D Bruce (On Haffkine s method of vaccination against asiatic cholera Brit M J 1 227 1893) described in detail the method of preparing the attenuated form of vaccine by treatment with phenol and the exalted form by guinea pig passage Their carbolized vaccine contained no live bacilli The seat of election is injection under the skin of the flank the first (attenuated) vaccine being given 3–5 days before the second (exalted) preparation

Haffkine later went to India where he used his method extensively under the sponsorship of the British and wrote his elaborate report to the government Haffkine believed that the vaccine was effective although the detailed figures are not very impressive He stated very conservatively however "The results obtained seem to indicate that in the inoculation we possess a means of effectively combating cholera epidemics I am of the opinion that this experimental stage is not yet in the advanced condition to be completely closed (p 47)

W Kolle (Zur activen Immunisierung des Menschen gegen Cholera Centralbl f Bakt 19 97 1896) was another pioneer in anticholera immunization In this important article he gives a valuable review of the theoretical basis for anticholera vaccination and quotes the fundamental experiments on which this is based In practice he injected first chloroform killed bacteria and 5 and 10 days later live virulent vibrios Later he seems to have changed the vaccine to a culture killed by heating to 58 C for 1 hour and preserved with 0 5 per cent phenol (P Krause and T Rumpf in Mense C *Handbuch der Tropenkrankheiten* [2d ed Leipzig J A Barth 1914] 3 299) This is essentially the type of vaccine used at present by the United States Army

M L Ahuja and Gurkirpal Singh ("Observations on cholera vaccine Indian J M Research 36 1 1948) give experimental support for the use of a mixture of Inaba and Ogawa strains in preparing the vaccine

The results of anticholera inoculation have however been variously judged Major Greenwood and G Udney Yule ("The statistics of antityphoid and anti cholera inoculations and the interpretation of such statistics in general Proc Roy Soc Med Sec Epidemiol & State Med 8 113 1915) for example who are expert statisticians give a careful mathematical analysis of published results While somewhat reserved Major Greenwood says in conclusion that so far as the data went the case in favour of anti cholera inoculation seemed to them strong

R Adiseshan C G Pandit and K V Venkatraman (Statistical evaluation of anti cholera inoculation as a personal prophylactic against cholera and its efficiency in the prevention and control of cholera epidemics " Indian J M Research 35 131 1947) found that the case incidence in 709 977 vaccinated persons was 1 57 per cent in 2 119 568 unvaccinated it was 16 20 per cent They thought that protection lasted for a minimum period of 6 months The vaccine contained both Inaba and Ogawa subtypes of Vibrio comma and was given in one dose of 8 000 000 organisms Quite recently L Kant ("An assessment of the value of cholera vaccine as used in a single dose mass inoculation [a field observation] J Trop Med 51 223 1951) in an observation covering 30 683 persons in India reaffirmed the protective action of the vaccine

outside the scope of this bibliography to review the subject in detail but this comprehensive summary goes into the chemical structure of vibrios their growth products their metabolism and chemical classification their antigenic structure etc The problems raised years ago by Pfeiffer (Ref 15) and others are not yet fully solved

23 FELSENFELD O DADTRADAY W S SACHEKO J I THORN W and NORSEN J In vitro sensitivity of recently isolated cholera vibrios to 10 antibiotics Proc Soc Exper Biol & Med 77:287 1951

With the advent of the newer antibiotics it was inevitable that they should be tried against cholera The present writers tested the action of 10 commonly used antibiotics against 53 recently isolated strains of V comma "The results showed a wide variation in susceptibility to these drugs according to the geographical origin of the vibrios" In a preliminary trial S C Seal S C Ghosal and M M Ghosh ("A preliminary trial of aureomycin [I V] in the treatment of cholera" Indian M Gaz 86 287 1951) found that in clinical use "no therapeutic advantage has been demonstrated" A Das S Ghosal, S K Gupta and R N Chandhuri ("Terramycin in cholera" Indian M Gaz 86 436 1951) in a somewhat more extensive trial found also that oxytetracycline (terramycin) made no significant difference in the effects of treatment Similar results were obtained by N R Koner and A N Sengupta ("Terramycin in cholera" Indian M Gaz. 83:469 1951) although they found that the first negative report of stool culture had been obtained earlier in oxytetracycline treated cases On the other hand E Olejnik and S Davidovitch ("Action of terramycin and chloromycetin on cholera vibrio in mice" Nature London 168 654 1951) found that mice inoculated intraperitoneally with V comma could be saved by both oxytetracycline and chloramphenicol provided that the drug was given within 5 hours after infection S C Lahiri ("Chemotherapy in cholera" Brit M J 1 500 1951) tried sulfaguanidine and other sulfonamides in cholera without reducing the mortality rate

The subject of antibiotics in cholera is treated editorially in the Journal of the Indian Medical Association (22 291 1953) and the writer concludes "The failure of these vibriocidal drugs once more emphasizes the immense importance both of prophylaxis and of the early restoration of body fluids on sound biochemical principles"

Apparently cholera comes like a storm and is quickly over and the main therapeutic measure remains the restoration of fluid and salts

24 AHUJA M L KRISHNAN K V PANDIT S R and VENKATRAMAN K V Laboratory diagnosis of cholera Indian J M Research 39 135 1951

Koch (Ref 11) laid the foundation of laboratory diagnosis of cholera The present note is an up-to-date statement of the best bacteriological procedure for isolating and identifying the cholera vibrio

Much earlier G Gaertner and A. Beck ("Über den Einfluss der intravenösen Kochsalzeinspritzung auf die Resorption von Flussigkeiten" Wien klin Wchnschr 6 563 1893) laid down the principles of the subject and advocated concentrated salt solution in cholera as rational to check the immense transuda tion of fluid into the bowel A W Sellards ("Tolerance for alkalies in asiatic cholera" Philippine J Sc 5 363 1910) emphasized the acidosis (increased tolerance for alkali) in cholera patients especially those who were anuric and he pushed the intravenous injection of solutions of sodium bicarbonate with what he thought were good therapeutic results In the light of modern studies of electrolytes and fluid balance it is difficult to evaluate this procedure Yet up to the present time intravenous fluids in some form remain the backbone of the treatment of cholera

20 GOODPASTURE E W Histopathology of the intestine in cholera Philippine J Sc 22 413 1923

Goodpasture made definitive studies of the histology of the intestine in cholera He found that one must have absolutely fresh material to avoid rapid post mortem changes He concluded that desquamation of epithelium was for the most part a post mortem change but that ante mortem desquamation might occur recognizable at autopsy by the presence of ulcers with acute inflamma tory exudate Anatomical evidence indicates that the great mass of vibrios is confined to the intestinal lumen and if toxic substances are formed there directly or indirectly as a result of their growth they are absorbed early in the disease through an anatomically intact mucosa"

21 [COUVY] Rapport sur les porteurs de germes de choléra Bull mensuel Office internat d'hyg publique Paris 25 1149 1933

W Kolle first showed years ago ("Über die Dauer des Vorkommens von Choleravibrionen in den Dejecten von Choleraeconvalescenten" Ztschr f Hyg u Infectionskr 18 42 1894) with daily cultures in 50 convalescents that the vibrios in all but 1 case disappeared in from 3 to 28 days

Couvy recognized the discharge of cholera vibrios by those in the incubation period or during convalescence but doubted the occurrence of chronic "healthy" carriers Probably some of those incriminated did not carry true pathogenic cholera vibrios At any rate the "chronic carrier" seems to play an insignificant part in the epidemiology of the disease This comprehensive report includes elaborate statistics from the literature The rarity of the persistence of the vibrios in convalescents is also brought out by the report of Y Y Ying ("The persistence of vibrios in cholera patients" Chinese M J 58 595 1940) who found in 200 cases of proved cholera that "a large proportion of cases (76 5 per cent) show positive stool cultures during the first week followed by a rapid decline thereafter being 21 5 per cent for the second 1 5 per cent for the third and 0 5 per cent for the fourth week Not a single case showed a positive culture after the fourth week"

22 LINTON R W The chemistry and serology of the vibrios Bact Rev 4 261 1940

As is usually the case the simple ideas of the early investigators in bacteriology have been displaced by highly complicated chemical and physical studies It is

BACILLARY DYSENTERY

Bacteriology	Refs 6 7 8 9 10 11 12 14
Carriers	Ref 17
Clinical	Refs 1 2 3 10
Contagion	Refs 2 3 4
Dysentery in infants	Ref 13
General	Refs 1 2 3
Pathology	Refs 1 2 3
Serum therapy	Ref 15
Toxin and antitoxin	Ref 16
Treatment with antibiotics	Ref 19
Treatment with sulfonamides	Ref 18

level of the more healthy portions that were interposed between them The small intestine and all the other parts were entirely healthy" (p 251) There are numerous pathological reports which shade off into other conditions but there is no doubt that Abercrombie reported many cases of true dysentery

2. BALY, William Gulstonian lectures [on dysentery] London M Gaz N.S 4:411 485 529 1847

It is difficult to select proper examples of bacillary dysentery from early nineteenth-century descriptions of dysentery and many justly famous accounts may have dealt largely with the amebic form Epidemics of non tropical dysentery were most frequent in armies jails and asylums and Baly s account is based on the disease as seen in "the great Government Prison of Milbank." The paper opens with a discussion of the pathology which pretty clearly deals with the bacillary and not the amebic type Baly describes lesions from cases of three degrees of severity "Dysentery in its most severe degree is frequently fatal in a very few days The inflammation affecting a large extent of the mucous membrane [of the colon] reduces it with extreme rapidity to the state of sphacelus" Baly reviews with great care the work of others "When the close relation subsisting between dysentery and suppurative disease of the liver in India is considered it cannot but appear remarkable that amongst the many hundreds of cases of dysentery which have occurred in the Milbank prison during the last seven years not one has been complicated with hepatic abscess" Baly was not of course dealing with amebic dysentery There follows an excellent clinical description in which, however the writer leans heavily on Sydenham Baly was totally at sea as to the cause of the disease The jail physicians concluded that it was due to a "local noxious influence" and with this Baly agreed "Here as in other instances where dysentery is endemic in prisons workhouses or lunatic asylums the cause really producing it is I believe a malaria rising from the surface of the ground around the building There are other influences from which dysentery might be supposed to arise namely diet the water used as drink, defective ventilation and defective sewage None of these however can have been the apparent cause of the disease in the Penitentiary" The reasons for this view are then gone into at length and show how a strong case can be erroneously built up The lectures conclude with remarks on treatment Baly relied mainly on "bloodletting the administration of calomel with opium and gentle aperients"

Such then was the state of knowledge on dysentery about a hundred years ago

3 WOODWARD Joseph Janvier Outlines of the chief camp diseases of the United States armies as observed during the present war Philadelphia J B Lippincott & Co 1863

This important book on "camp disease in the Civil War is also of interest as indicating the general philosophy of epidemic disorders at the time Thus Woodward divides disease into "1 Miasmatic diseases 2 Enthetic diseases 3 Dietic diseases" Most sickness which we now know to be infectious is placed in the miasmatic group "The word miasmatic is therefore used in its original broad sense to include all disease due to the influence of miasms whether those arising from telluric sources such as vegetable decomposition (koino miasmata)

BACILLARY DYSENTERY

THE history of dysentery is obscured by the confusion which existed between the bacillary and amebic types before the recognition of the causal agents Various observers noted however with keen clinical insight that the types of dysentery seen in the tropics were often associated with liver abscess whereas such a lesion was conspicuously absent in the dysenteries of temperate climates However one is not certain with many of the early articles whether the writer was dealing with amebic or bacillary dysentery

The history of the subject is summarized by Leonard Rogers (*Dysenteries Their Differentiation and Treatment* [London Oxford University Press 1913]) and by Philip Manson Bahr (*The Dysenteric Disorders* [2d ed Baltimore Williams & Wilkins Co 1943]) The monograph by W C Davison ("A bacteriological and clinical consideration of bacillary dysentery in adults and children Medicine 1 389 1922) is a storehouse of information on the subject with a definitive bibliography to date of over five hundred titles Hirsch (Ref 5) gives a full account of the older epidemics everywhere whereas outbreaks in Great Britain are dealt with by Charles Creighton (*A History of Epidemics in Britain* [Cambridge Cambridge University Press 1894] 2 747)

The article by F S Cheever Bacillary dysentery and the Shigella" in R J Dubos *Bacterial and Mycotic Infections of Man* (2d ed Philadelphia J B Lippincott Co 1952) page 437 is specially strong on the bacteriological intricacies of the subject an authoritative modern discussion of the whole problem is to be found in G S Wilson and A A Miles in Topley and Wilsons *Principles of Bacteriology and Immunity* (4th ed Baltimore Williams & Wilkins Co 1955) 2 1760

1 ABERCROMBIE *John Pathological practical researches on diseases of* the stomach the intestinal canal the liver and other viscera of the abdomen Philadelphia Carey & Lea 1830[1]

This book contains Abercrombies justly famous description of acute dysentery "There is generally pain in the abdomen in some cases permanent in others occurring in paroxysms of tormina and it is usually accompanied by considerable tenderness when rather severe pressure is made but distinct from the acute sensibility which accompanies inflammation of the peritoneum There is more or less irritability of the bowels sometimes in the form of diarrhoea with copious *stools* and sometimes of *painful tenesmus with frequent scanty* discharges of bloody mucus There is generally some degree of fever The evacuations vary exceedingly in their character consisting in some cases of small quantities of bloody mucus or almost pure blood (p 242) The general description is supported by autopsy reports for example "The whole tract of the colon appeared moderately and uniformly distended Internally it showed most extensive disease of the mucous membrane This consisted of portions of the membrane of various forms and degrees of extent being of a fungous appearance and bright red colour and sensibly elevated above the

[1] *The English edition* (1827) was not available to us

phoid and other infectious diseases however by the fact that the dysentery poison produces demonstrable pathological changes only in the large bowel

The dysentery poison has to be sure not been directly demonstrated to be an organic living substance but arguments already discussed in connection with Typhoid and Cholera influence us to regard dysentery also as an infection of the body by a specific species of lower vegetable organism and to speak of a dysentery germ just as we have talked of a typhoid germ and a cholera germ The dysentery germ grows thrives and multiplies outside of the human body and persons exposed to its location are in danger of sickening with dysentery Favorable conditions for growth and multiplication of the dysentery germ are present in tropical and subtropical regions there dysentery rages over large areas It appears that the dysentery germ under favorable conditions always reproduces itself in the body of an infected individual and that the dejections of those ill with dysentery contain the contagion or a precursor of it for while not proved it is more than probable that lavatories bedpans and klysters which dysentery patients have used can transmit the disease to healthy contacts" Cold wet and eating unripe fruit are merely incidents which may predispose to infection with the specific germ which is the only direct cause

5 HIRSCH August Handbuch der historisch geographischen Pathologie 3:195 2d ed Stuttgart Ferdinand Enke 1883

This article on dysentery contains first a historical outline and next a comprehensive summary of the geography of the disease both heavily documented There then follows an elaborate enumeration of epidemics and finally a discussion of the influence of diet temperature etc Hirsch even as late as 1886 is still conservative about a bacterial cause but the article is nonetheless of great value

6 CHANTEMESSE and WIDAL F Le Microbe de la dysenterie épidémique Semaine med 8:153 1888

Among the early claims for isolation of the microbe of dysentery the most plausible is that of Chantemesse and Widal Although the description is not complete all the features mentioned are compatible with dysentery bacilli "The presence of the bacillus which we describe in the intestinal wall the mesenteric glands and the deep organs of a man dead of an acute relapse of dysentery the finding of it in the stools of five patients with dysentery its absence in healthy man the lesions which it gives rise to in the intestines and viscera of guinea pigs plead in favor of its specificity

Years later during the course of a polemic on priority of discovery of dysentery bacilli which was waged between Shiga and Kruse Chantemesse and Widal ("Ueber die Prioritat der Entdeckung des Ruhrbacillus" Deutsche med Wchnschr 29 204 1903) again took up the cudgels and claimed priority for themselves While it is highly likely that they dealt with dysentery bacilli an impartial reader must admit that their evidence was not fully conclusive

7 SHIGA Kiyoshi Ueber den Erreger der Dysenterie in Japan Centralbl f Bakt 23 599 1898

The seriousness of the dysentery problem in Japan where there were ninety thousand cases with twenty thousand deaths in 6 months impelled Shiga to

or those produced by the decomposition of matters derived from the human body (idio-miasmata) " Further under conditions determining the character of camp diseases there are sections on Malarial Influences Crowd Poisoning and 'The Scorbutic Taint In spite of these primitive ideas on communicable disease Woodward s objective descriptions are excellent Camp diarrhea is divided into simple diarrhea acute enteritis and acute dysentery mainly it would seem on a basis of severity of symptoms But even very acute cases seemed less severe the malignant dysentery of European armies had not yet made its appearance among our troops " Any of the causes capable of producing acute enteritis may give rise to dysentery with those who are susceptible Indigestible food unhealthy water exposure to heat sleeping on damp ground changes of temperature and other causes may give rise to this disorder Malarial influence is a potent predisposing cause a scorbutic habit is also an important predisposing cause" (p 223) An excellent description of the clinical features and of the pathological changes follows No liver abscesses were encountered Treatment began with a purge followed by Dover s powder and astringents such as acetate of lead and sulfate of copper if simple treatment did not suffice A limited plain diet is emphasized such as boiled milk with rice beef essence and mucilaginous or acidulated drinks "There can be no doubt however that in moderate doses ipecuanha is a valuable remedy in the early stages of the disease both from its action upon the skin and from the astringent effect upon the bowels

We can see then how slowly progress was being made in both the understanding and the treatment of dysentery Woodward later contributed a monumental volume on the *Alvine Fluxes* to the "Medical and Surgical History of the War of the Rebellion (1861–65) Part II Vol I being the second medical volume This tremendous folio of nearly nine hundred pages deals in intimate detail with every phase of the subject—statistical clinical pathological and epidemiological "These disorders occurred with more frequency and produced more sickness and mortality than any other form of disease Soon no army could move without leaving behind it a host of the victims They crowded the ambulance trains the railroad cars the steamboats In the general hospitals they were often more numerous than the sick from all other diseases and rivalled the wounded in multitude There was a total of 1 739 135 cases of dysentery during the war with 44 558 deaths With regard to the question "Is dysentery contagious? Woodward (p 646) gives a masterful analysis of the literature and the contradictory opinions of others "For myself I strongly incline to adopt the view of the contagion of the stools for at least a certain class of dysenteric cases yet I frankly admit the recorded evidence on this head is by no means so conclusive as that which we possess with regard to typhoid fever The volume concludes with a long section on therapy in which the merits of every conceivable drug and agent are discussed

4 NIEMEYER Felix Lehrbuch der speciellen Pathologie und Therapie chap xiv p 747 article "Dysentery" 7th ed Berlin August Hirschwald 1868

Bitter arguments went on for years as to whether dysentery was contagious and evidence pro and con was assembled Niemeyer seems to have been one of the first however to make a clear modern precise statement in favor of contagion Dysentery is an infectious disease it is to be distinguished from ty

the observations to which he refers so freely are undocumented Next come clinical and pathological descriptions of various types of dysentery the pathological histology of the acute non amebic disease is precisely delineated. Flexner worked in the Philippine Islands and dealt with soldiers in the American army of occupation Stool cultures disclosed two bacillary types Type I corresponded in all its features with the bacillus of Shiga (Ref 7) "That the bacillus is identical with the organism obtained by Shiga in the epidemic of dysentery which prevailed in Japan there can be no reasonable doubt" Flexner also found often as the predominating organism one whose "properties vary somewhat but agree well with those of group B coli communis" Agglutination tests and animal inoculations with the Type I organism correspond pretty well with those described by Shiga including the fact that the dead cultures were "toxic" As to specific serotherapy Flexner was optimistic but reported no details He concluded "It is only natural to ask whether the foregoing considerations justify a belief in a specific organism of dysentery My own sense is against that belief although it must be conceded that the varieties of the disease are fewer than the clinical and pathological anatomical conceptions of the time would lead one *to suppose I think I have shown that tropical dysentery consists of a* bacillary and an amoebic form It is important to know whether the epidemic disease is more uniform in its causation and pathological anatomy The studies of the Japanese disease by Shiga are highly suggestive of this conclusion but additional observations will be required before we can accept as final his conclusions" A more precise account of this work appeared simultaneously (Simon Flexner "The etiology of tropical dysentery" Centralbl f Bakt. 28:625 1900)

Shortly after E B Vedder and C W Duval ("The etiology of acute dysentery in the United States" J Exper Med 6 181 1901) working at the instigation of Flexner studied dysentery in the United States and concluded that the disease here was "due to a bacillus undistinguishable from that obtained from the epidemics of dysentery in several other parts of the world and that sporadic and institutional outbreaks were caused by this same organism which was in fact, the *Bacillus dysenteriae* of Shiga

9 KRUSE W Ueber die Ruhr als Volkskrankheit und ihren Erreger Deutsche med Wchnschr 26 637 1900

Kruse studied an outbreak of acute dysentery in the little industrial town of Laar In fresh cases the colonies of dysentery bacilli "were so numerous that they impressed one as being in pure culture and the coarser colonies of colon bacilli were practically displaced" The organism failed to produce gas and, in contrast to Shiga's seemed to be less motile Animal inoculations "were all negative" Although the organisms made small animals ill "they cannot achieve a local lesion in the large bowel" The organisms were agglutinated by the sera of patients after the seventh day It is evident that Kruse's organism was closely related to those of Shiga and of Flexner

10 STRONG R P and MUSGRAVE W E The bacillus of Philippine dysentery J A M A 35 498 1900

Strong and Musgrave made important studies on dysentery in the American forces in the Philippines simultaneously with those of the Flexner commission

look for the causal agent Since animals were resistant to the production of dysentery Shiga sought an organism in the dejecta of patients which would be agglutinated by their blood serum similarly to the Widal test in typhoid fever He reports finding in the stools and internal organs of thirty six cases of dysentery an organism which was agglutinable by the serum of dysentery patients "The bacillus is short rounded at both ends and sluggishly motile Morphologically it resembles the typhoid bacillus and is gram negative" He then describes cultural reactions on various media and points out that dextrose was not fermented The bacillus was uniformly found in the dejecta of thirty four patients and in the bowel wall of two men dead of dysentery He was unable to obtain the organism from healthy people or from those with other diseases The agglutinative reaction was also found to be specific Infiltration followed by suppuration resulted from subcutaneous injection of cultures into guinea pigs Introduction of culture into the stomach of young dogs or cats was followed in 1 or 2 days by slimy stools Subcutaneous injection into man of killed culture produced a general febrile reaction with painful induration at the site of inoculation and the serum developed agglutinins within 10 days "From the above mentioned grounds one must assume that this bacillus has the most intimate connection with dysentery and indeed I feel that one may regard this bacillus as the cause of dysentery

In another more detailed paper (K Shiga "Ueber der Dysenterie bacillus [Bacillus dysenteriae] Centralbl f Bakt 24 817 870 913, 1898) Shiga opens with an analysis of previous attempts to isolate a living agent from cases of dysentery He thought it probable that amebae played a role in tropical dysentery but questioned the significance of the numerous claims that had been made for one or another bacterium He then describes in great detail the morphological and cultural characters already mentioned in the first paper He laid great stress on the specific agglutination test From the bodies of two patients dead of dysentery the bacilli were found in large numbers in the wall of the bowel which was the seat of an acute process Where the process was old there were few colonies of dysentery bacilli but many of *B coli* and strepococci Small animals receiving large subcutaneous doses of dysentery bacilli died in a few days a dog fed an entire agar slant of culture developed diarrhea with recovery of dysentery bacilli and died in 5 days Chickens and pigeons seemed unaffected by injection or feeding of bacilli Small animals who received injections of killed dysentery bacilli developed specific agglutinins in their blood Shiga himself after an injection of one-twelfth of an agar slant of heat killed bacilli developed chills and fever and a painful induration at the site of inoculation which he concluded was due to toxin produced by the bacilli since on incision no organisms were recovered He predicted that protection would be achieved by the development of proper sera

As in the history of so many infectious diseases the worker who first isolated the correct causal organism skimmed the cream" and left relatively little for his successors to prove

8 FLEXNER Simon On the etiology of tropical dysentery Philadelphia M J 6 414 1900 also in Bull Johns Hopkins Hosp 11:231 1900

In this masterly lecture Flexner first reviews the confused medley of etiological claims—amebic and bacterial—of the cause of severe dysentery Unfortunately

whereas those of Shiga and of Flexner were motile and flagella bearing Vedder and Duval (Ref 8) also raised the question of whether there might not exist in various strains those "individual differences and peculiarities such as may readily exist within the limits of a single species" However Martini and Lentz were the first to claim significant differences among the various dysentery bacilli They pointed out that agglutination tests with convalescent sera were inadequate to answer the question and they prepared hyperimmune sera by immunization of goats They showed that the bacilli of Shiga of Kruse of Flexner (New Haven strain) and of some others fell into one group whereas those of Flexner (Manila) of Strong of Kruse (asylum strain) and others fell into another Lentz ("Vergleichende culturelle Untersuchungen uber die Ruhr bacillen und ruhrahnliche Bacterien nebst einige Bemerkungen uber den Lakmusfarbstoff *ibid* p 559) tried out growth of various strains on sugars and found definite differences Mannite for example was unaffected by Shiga and Kruse s strains whereas it was fermented by Flexner and Strong s This work therefore changed the point of view about the identity of all dysentery strains and showed that there were important differences which subsequent work has amply confirmed Thus W H Park K R Collins and M E Goodwin ("The dysentery bacillus group and the varieties which should be included in it" J M Research 11:553 1904) found by agglutination tests that most dysentery bacilli fell into three serologically different groups The first type isolated by Shiga did not ferment mannite the second fermented mannite but did not split maltose or saccharose The third type fermented mannite but also maltose and saccharose Park suggested the name "dysentery bacilli for the type isolated by Shiga and "para-dysentery" for all others P H Hiss Jr ("On fermentative and agglutinative characters of bacilli of the dysentery group " J M Research 13 1 1904) found using similar methods that these organisms fell into four groups one of which was represented by the organism he described "The marked pathogenicity of the Shiga Kruse organisms as compared with that of the mannite fermenting organisms and the differences in the specific reactions called forth in the animal body by these various organisms make it not improbable that detectable differences may exist in the clinical or pathological picture induced by them " This prediction has been amply fulfilled This paper begins with a definitive critical analysis of all bacteriological claims from Shiga s original paper to date (1904)

To appreciate however the intense interest and the elaborate work which was stimulated by the questions of the etiology of dysentery at the turn of the century a major disease both of adults and children the original reports must be read

13 DUVAL C W and BASSETT V H The etiology of the summer diarrhoea of infants a preliminary report Am Med 4:417 1902

So-called summer complaint was a common affection of babies during the hot months on the Atlantic seaboard Duval and Bassett were able to isolate dysentery bacilli which they considered identical with those of Shiga from 42 cases of typical "summer complaint" The specific organism was secured also from scrapings of the intestinal mucosa at autopsy and in one case from the mesenteric glands and liver The organism was obtained however with difficulty from mild cases and those of long duration on account of its presence in small

They defined the disease as an acute infectious disease characterized anatomically by an extensive superficial necrosis of the mucosa and by hyperplasia and hemorrhagic infiltration of the lymph follicles of the large intestine with induration and thickening of its walls by hemorrhagic swelling of the adjacent mesocolic glands and often by parenchymatous changes in other organs The Bacillus dysenteriae is present in the acute stage of the disease both in the discharges and in the superficial necrotic layer of the intestinal mucosa Clinically the disease is marked by an acute onset by very frequent mucous bloody stools accompanied by an intense tenesmus and by an abrupt termination either in death—usually in from four to fifteen days—or by a gradual improvement from which an early recovery takes place or the disease may apparently pass into a subacute stage " They thought that infection probably occurred through contaminated water and food They described in detail the reactions of the bacillus which they isolated and which they regarded as similar to if not identical with that isolated by Shiga in Japan

The paper concludes with an admirable clinical description "The period of incubation probably lasts not over 48 hours In one case in which a pure culture of the organism was swallowed symptoms of dysentery began to appear after 24 hours The onset of the disease is usually abrupt Often a patient goes to bed feeling perfectly well during the night he is suddenly attacked with dysentery and it is not infrequent for these cases to have from twenty to forty stools during the night generally within forty eight hours or a shorter time the stools consist of nothing but reddish bloody mucus Microscopically these discharges consist of many red blood cells leukocytes epithelial cells and large epithelioid cells The temperature may often reach 103 or 104 F or it may not rise above 102 F

11 FLEXNER Simon A comparative study of dysenteric bacilli Centralbl f Bakt 30 449 1901

During the year after Flexner (Ref 8) reported his work a number of observers isolated bacilli from dysentery cases (Strong Ref 10 Kruse Ref 9) It occurred to Flexner to compare these various organisms and to see whether they were all of one type Although some very minor differences were noted Flexner concluded "The results of this comparative study leaves [sic] no doubt of the identity of the several bacilli with which I have worked They indicate moreover that the acute dysenteries whether in the far East Germany or the West Indies are due to the same organism The justification for the view of a specific organism of dysentery would therefore seem to be near at hand

There is little doubt in my mind that the acute epidemic dysenteries of this country are caused by the same micro-organism The same material appeared in England (Brit M J 2 786 1901)

12 MARTINI E and LENTZ O Ueber die Differenzierung der Ruhr bacillen mittels der Agglutination Ztschr f Hyg u Infectionskr 41 540 1902

Following the work reported above (Ref 11) it was pretty generally accepted that dysentery strains the world over were identical Further isolations by others summarized by Martini and Lentz seemed to confirm this view However Kruse pointed out that his strain was non motile and had no flagellae

lary dysentery" J A M A 132:362 1916) devised a method of producing bacillary dysentery in man and then showed that human volunteers vaccinated with heat killed and ultraviolet irradiated vaccine showed no significant immunity against experimental infection" which was effectively controlled by sulfadiazine

16 TODD Charles On a dysentery toxin and antitoxin J Hyg 4 480 1904

Although Shiga (Ref 7) had already referred to the toxicity of dysentery bacilli Todd ("On a dysentery antitoxin" Brit M J 2 1456 1903) was one of the first to recognize clearly a soluble exotoxin in distinction to the poisonous effects of whole or ground up bacterial bodies Todd re-emphasized the essentially local growth of the bacilli in epidemic dysentery from which toxin is absorbed to produce severe symptoms Todd was able to isolate the soluble toxin from old cultures of *B dysenteriae* (Kruse) to which horse and rabbit were highly susceptible whereas guinea pig rat and mouse were very resistant He produced in horses antitoxic sera which seemed to have a high protective effect. The soluble toxin seemed to be produced only by the Shiga type of bacilli since attempts to isolate it from other strains of dysentery bacilli were unsuccessful Much more work was done but P K Olitsky and I J Kligler ("Toxins and antitoxins of Bacillus dysenteriae Shiga" J Exper Med 31:19 1920) appear to have been successful in separating an exotoxin which produced paralyses and central nervous system lesions in rabbits as well as an endotoxin which injured the bowel and caused dysenteric symptoms Sera containing antitoxins against both varieties were produced in horses A modern authoritative summary of the problems of antigenic structure somatic antigens and toxins and classification is to be found in Cheever's article (*loc cit*)

17 SELIGMAN E Zur Bacteriologie der Ruhr im Kriege Munchen med Wchnschr 63:68 1916

The question of how long dysentery bacilli persisted in the stools was one of obvious importance Seligman in the German army made stool cultures from fresh material from dysentery patients Although only 38 per cent of all cases were positive dysentery bacilli were isolated in 70 per cent during the first week of the disease in 53 per cent in the second week, in 18 per cent in the third whereas no culture was positive in the fourth week. Others such as C J Martin and F E Williams ("The chance of recovering dysentery bacilli from the stools according to the time elapsing since the onset of the disease" Brit. M J 1 447 1918) reported similar results Whereas of cultures made during the first 5 days 68 0 per cent were positive only 17 4 per cent yielded dysentery bacilli from the sixth to the tenth day An occasional culture was positive up to the fiftieth day Apparently the dysentery bacilli are "overwhelmed by a host of intestinal organisms as the acute dysenteric process subsides J Schurer ("Ueber die Pathogenese der Dauerausscheider und Bazillentrager Berl klin Wchnschr 57 106 1920) takes up the question of prolonged carriage and believes that when this occurs there is a local focus of chronic inflammation in the bowel in which the bacilli grow and from which they are discharged W Fletcher and D L Mackinnon ("A contribution to the study of chronicity in dysentery carriers" M Res Council Spec Rep Ser

numbers among the normal intestinal bacteria This was a most important study however since it linked the summer diarrheas of babies with acute epidemics of dysentery in adults Shortly after M Wollstein ("The dysentery bacillus in a series of cases of infantile diarrhoea" J M Research 10 11 1903), working in New York found organisms of the Flexner (Manila) type in infants and young children "The bacilli are present in the stools for a period of two to three weeks but may remain for a longer time" These findings were confirmed by numerous other workers and are reviewed by W C Davison ("Bacillary dysentery in children" Bull Johns Hopkins Hosp 31 225 1920) Davison gives a fine clinical description of the disease in infants

14 HISS P H and RUSSELL, F F A study of a bacillus resembling the bacillus of Shiga from a case of fatal diarrhoea with remarks on the recognition of dysentery typhoid and allied bacilli M Rec 63 357 1903

In this paper Hiss and Russell describe the isolation and characteristics of the dysentery bacillus which has ever since been recognized as representing a definite type The organism fermented marmite and was specifically agglutinated The patient from whom this bacillus was isolated was a child of one year with rather mild diarrheal symptoms without gross blood in the stools He failed progressively and died in two weeks

From this point on the isolation and differentiation of innumerable races of dysentery bacilli becomes a matter more of bacteriology than of medicine and cannot be pursued further in this bibliography Those interested are referred to the reviews of Erwin Neter ("The genus Shigella" Bact Rev 6 1 1942) and of Wilson and Miles (*loc cit*)

15 KRUSE Die Blutserumtherapie bei der Dysenterie Deutsche med Wchnschr 29 6 49 1903

It is difficult for one to realize today how much confidence was placed in the efficacy of vaccine and serum therapy in infectious disease at the turn of the century Almost immediately after the dysentery bacilli were isolated attempts at specific immunotherapy were undertaken Kruse tells of early efforts to produce potent sera the difficulty of finding a suitable animal the toxicity of cultures etc Nonetheless he concludes that beneficial effects are obtained insofar as the severity of the disease is mitigated duration and convalescence shortened and mortality lowered A little later Shiga ("Ueber die Prioritat der Entdeckung des Ruhrbacillus und der Serumtherapie bei der Dysenterie" Deutsche med Wchnschr 29 113 1903) claimed priority and stated that for several years the mortality under serum therapy was cut to one third that of the untreated disease With regard to prophylactic vaccination with killed cultures on the other hand Shiga ("Ueber Versuche zur Schutzimpfung gegen die Ruhr" *ibid* p 327) early obtained no conclusive proof of effectiveness An immense amount of work on immunotherapy was subsequently done with results which were variously judged The final verdict however as summarized for example by Cheever (*loc cit*) is that these procedures are probably ineffective and useless At any rate they have not stood the test of time and neither vaccines nor sera are any longer advised Thus H J Shaughnessy R O Olsson K Bass F Friewer and S O Levinson ("Experimental human bacil

19 HARDY A V MASON R P and MARTIN G A The antibiotics in acute bacillary dysentery Ann New York Acad Sc. 1952 p 1070

The writers had an opportunity in Korea to treat large numbers of cases of bacillary dysentery under well-controlled conditions with various antibiotics Aureomycin terramycin and chloromycetin as well as sulfadiazine and non specific measures were used in different patients The three antibiotics all were about equally effective and within 7 days 95–98 per cent of the patients were convalescent and dysentery bacilli were no longer isolated The figures for sulfadiazine and non specific therapy on the other hand were only 60 and 62 per cent "The differences in sigmoidoscopic findings at the fourth day were particularly impressive Most of those on nonspecific therapy still had the hyperemic edematous bowel probably with bleeding points a copious mucopurulent exudate microscopically loaded with pus cells In patients on antibiotics the hyperemia edema bleeding and exudate were gone and the mucous membrane was clear except for fading submucosal hemorrhagic areas Clinically it was evident that the three antibiotics were all highly effective" F S Cheever ("The treatment of Shigellosis with antibiotics" Ann New York Acad Sc., 1952, p 1063) gives an authoritative review of the whole subject of drugs and antibiotics in bacillary dysentery

No 27 1919) divide carriers into those harboring Shiga bacilli and those with Flexner bacilli The former may continue to be carriers for months or years after the critical attack and are usually invalids with chronic or intermittent bowel symptoms The Flexner carriers are likely to be intermittent but carriage may persist for years even after a very mild initial attack The proportion of carriers among convalescents was small but some were remarkably persistent. "In the group of 847 non dysentery convalescents there were 9 carriers of dysentery bacilli (1 06 per cent) and 6 of these gave a history of dysentery" These nine were all Flexner carriers

The point of all this is that, whereas dysentery bacilli usually disappear rapid ly from the stools they occasionally persist at times without an evident lesion

18 MARSHALL E K Jr BRATTON A C EDWARDS L B and WALKER E Sulfanilylguanidine in the treatment of acute bacillary dysentery in children Bull Johns Hopkins Hosp 68 94 1941

The development of the sulfonamides created a revolution in the therapy of bacillary dysentery E K Marshall Jr A C Bratton H J White and J T Litchfield Jr (Sulfanilylguanidine a chemotherapeutic agent for intestinal infections Bull Johns Hopkins Hosp 67 163 1940) studied the pharmaco logical qualities of sulfanilylguanidine and found it appropriate for intestinal infections insofar as it was poorly absorbed from the intestinal tract In a clinical study of the drug in cases of bacillary dysentery promising results were obtained especially if the drug was used early Furthermore L A Rantz and W M M Kirby (The use of sulfaguanidine in the treatment of dysentery carriers J A M A 118 1268 1942) found that dysentery bacilli disappeared from the stools during treatment with this drug and did not return during periods of observation of from 30 to 90 days C J Smith *et al* ("Acute bacillary dysentery [Flexner] treatment with sulfaguanidine and succinylsulfathiazole J A M A 121 1325 1943) considered succinylsulfathiazole an even safer and more effective drug T L Roberts and W B Daniels ("Succinylsulfathiazole in the treatment of bacillary dysentery" J A M A 122 651 1943) on the contrary found that succinylsulfathiazole produced no amelioration of the illness nor did it shorten its duration This would be expected in an illness of only four days duration But the carrier rate was only 2 6 per cent in the treated cases as against 18 2 per cent in a comparable untreated group A V Hardy W Burns and T De Capito ("Studies of the acute diarrheal diseases cultural observations on the relative efficacy of sulfonamides in Shigella dysen teriae infections Pub Health Rep 58 689 1943) compared the efficacy of sulfaguanidine sulfasuxidine sulfadiazine and sulfathiazole There were mod erate variations only in the efficacy of the four sulfonamides Later A V Hardy and J Watt (Newer procedures in laboratory diagnosis and therapy in the control of bacillary dysentery Am J Pub Health 44 503 1944) summarized the whole question and concluded "Well absorbed sulfonamides as well as poorly absorbed preparations are effective in Shigella infections and are recommended It is obvious therefore that variations in response occur with different strains of Shigella and in different outbreaks so that no prep aration is proved to be consistently the best

Section 4

PLAGUE

Bacteriology	Refs 2 3 4 7
Clinical	Refs 1 3 4
Epidemiology	Ref 11
General	Refs 1 3 4
Immunity	Ref 8
Pathology	Refs 1 4 9
Pneumonic plague	Ref 6
Rats (role in plague)	Refs 7 10
Sylvatic plague	Ref 12
Transmission (fleas)	Refs 7 10
Treatment, antibiotics	Refs 14 15 16
Treatment, serum	Ref 5
Treatment sulfonamide	Ref 13
Vaccination	Refs 5 8

ever be given The great plague in London in 1665 for instance has been immortalized by Defoe in his *Journal of the Plague Year* (many editions) as well as by Pepys in the diary The contemporary bills of mortality (*Londons Dreadful Visitation or a Collection of All the Bills of Mortality for This Present Year Etc by the Company of Parish Clerks of London* (1665)) bring vividly before one the course of this epidemic Walter G Bell's book *The Great Plague in London 1665* (London John Lane The Bodley Head Ltd 1924) is a classical study of every phase of this outbreak well illustrated with full bibliography Along with this material *The Plague in Shakespeare's London* by F P Wilson (Oxford Clarendon Press 1927) is of great interest

When plague disappeared from Europe in the early eighteenth century the Continent was left in a state of terror lest the scourge again gain a footing Fear of the plague and the elaborate quarantine measures adopted are all illustrated by the events connected with Shelley's death and burial

When Shelley and his companion Edward Ellecker Williams were drowned and later were washed up on the Tuscan shore the local officers simply covered the bodies with quicklime Trelawney the friend of Shelley with Byron and Leigh Hunt had to exercise the greatest efforts to gain permission even to approach the bodies and to cremate them "After a variety of applications and correspondence with Mr Dawkins Secretary of Legation the English consul Falkener and the Governor of Leghorn—I obtained from the latter an order to the officer on the coast—commanding the lookout tower nearest to that part of the beach on which Williams had been found and buried—to deliver to me his body—and an officer of the Sanitair Office to accompany me and see that it was consumed to ashes Mr Dawkins likewise obtained me an order of the like purport and condition from the Lucchese government—for the body of Shelley found and interred on their coast I proceeded on shore and after showing my bill of health I was allowed to land The captain of the port with another officer received me on shore" They then proceeded to the spot where the body lay "At equal distances along the coast stood high square towers for the double purpose of preventing smuggling and enforcing the quarantine laws the latter being here severer than in any part of the world We then with instruments made for the purpose of dragging wrecked seamen out of the sea—for you are on no account allowed to touch a body—we dragged the remains out of the grave The soldiers who appeared superstitiously fearful had withdrawn themselves as far as possible" (*Letters of Edward John Trelawney ed H Buxton Forman* [Oxford Oxford University Press 1910] p 4) One can picture the scene as Trelawney has so vividly described it—the hot yellow beach the glittering sunshine the blue sky the pines in the background and the colorful uniforms of the frightened soldiers shrinking back from the proceedings

No better popular account of the plague and the reaction of the people to it can be found than that of Kinglake in his remarkable book *Eothen or Traces of Travel Brought Home from the East* (London John Ollivier 1844)

"I had come to the end of this wheel going Europe and now my eyes would see the Splendour and Havoc of the East

"The two frontier towns are less than a cannon shot distant and yet their people hold no communion The Hungarian on the North and the Turk and Servian on the southern side of the Save are as much asunder as though there

PLAGUE

THE bibliography of plague presents many difficulties A disease of such striking clinical and epidemiological features and of such malignancy could hardly fail to strike the popular fancy and to call forth a colossal mass of writing from ancient times on We shall not attempt to deal with the narrow historical aspects of plague but rather refer the reader to the monumental work by Georg Sticker (*Ablandlungen aus der Seuchengeschichte und Seuchen lehre* [Giessen Alfred Topelmann 1908] Vol 1, Parts 1 and 2) which contains a bibliography of some two thousand titles B M Lersch s *Geschichte der Volksseuchen* (Berlin S Karger 1896) contains much valuable material on plague epidemics A dependable and authoritative account is given in August Hirsch s invaluable monograph *Handbuch der historisch geographischen Pathologie* (2d ed Stuttgart Ferdinand Enke 1881) 1 349 (English translation by Creighton [London New Sydenham Society 1883] 1 494) Epidemics of plague in England are also told about in an interesting fashion in Charles Creighton *A History of Epidemics in Britain* (Cambridge Cambridge University Press 1891) 1 470 A semipopular but readable account is also to be found in H Harold Scott s *A History of Tropical Medicine* (Baltimore Williams & Wilkins Co 1939) 2 702

Authoritative modern reviews of the bacteriology and immunology of plague are those by G F Petrie in *A System of Bacteriology in Relation to Medicine* (London 1929) Vol 3 chap viii p 137 and by G S Wilson and A A Miles in Topley and Wilson s *Principles of Bacteriology and Immunity* (Baltimore Williams & Wilkins Co 1946) Vol 2, chap 73 p 1627 Among general books on the subject there are to be mentioned especially *Plague* by Wu Lien Teh J W H Chun R Pollitzer and C Y Wu (Shanghai Station China National Quarantine Service 1936) and *Plague* by R Pollitzer (Geneva World Health Organization 1954) These two works deal with every phase of the subject and have comprehensive bibliographies

In addition invaluable and extensive material is to be found in the reports of the plague commissions sent to the site of outbreaks by various nations to wit

Austrian Commission *Denkschriften d k Akad d Wissenschaften Wien 1898–1900* (3 vols)

German Commission "Bericht uber die Thatigkeit der zur Erforschung der Pest im Jahre 1897 nach Indien entsandten Kommission erstattet von Dr Gaffky Dr Pfeiffer Dr Sticker Dr Dieudonné Arb a d k Gsndhtsamte Berlin Vol 16, 1899

British Commission Special reports in the Journal of Hygiene in the form of extra "Plague numbers" and "Plague supplements 1906–15

International Commission (Chinese) *Report of the International Plague Conference Held at Mukden April 1911* (Manila Bureau of Printing 1912)

There is an immense literature of books and articles on individual outbreaks of plague ranging all the way from critical scientific accounts to popular stories We cannot attempt to document this material An example or two may how

A little later Yersin ("La Peste bubonique à Hong Kong" Ann Inst Pasteur 8:662 1894) wrote a more formal report "When I arrived [at Hong Kong] more than 300 Chinese had already succumbed. These are the symptoms sudden onset after incubation of 4-6 days shock, and prostration Strong fever often with delirium A bubo in the groin generally appears in the first day reaching the size of a hen s egg Death occurs usually by 48 hours often sooner If life is prolonged beyond 5 or 6 days the outlook is better" In some cases the bubo does not have time to form one then observes mucous membrane hemorrhages and petechiae in the skin Mortality is high—about 95 per cent in the hospitals In the infected quarters many dead rats litter the ground. The lodgings of the Chinese of the poor classes contain an unbelievable number of people Many are without windows and below the level of the ground The only remedy would be to burn up the Chinese town" It has been observed that plague before striking human beings acts with great intensity on mice rats buffaloes and pigs

He describes again in more detail the isolation of the organism "The ends of the bacilli stain more intensely than the centers sometimes they seem surrounded by a capsule" White transparent colonies developed on gelatin The bacillus also grew well on coagulated serum The appearance in broth was characteristic clear liquid with grumous deposits on the walls and bottom of the tube Examined under the microscope the cultures showed chains of short bacilli If one opened the body of a guinea pig dead of plague one found hemorrhages in the abdominal wall pink edema at the site of inoculation and around the neighboring glands which were large and filled with bacilli The intestine was often hyperemic the adrenals congested the kidneys violaceous the liver large and red the spleen very large frequently a sort of eruption of little miliary tubercles Yersin noted in subcultures that after several days large colonies appeared which showed a great reduction in virulence on injection into animals Dead rats found in the houses and streets always contained the microbe in immense numbers "Plague is then a disease both contagious and inoculable It is probable that rats constitute the principal vehicle but I have shown that bats can also serve as agents of transmission" He thought that the avirulent strains which developed in cultures were capable of conferring immunity against plague on an animal and stated that he would report further on this point [1] It is obvious that Yersin skimmed the cream of plague studies

3 KITASATO S The bacillus of bubonic plague Lancet 2:428 1894

Kitasato who had been sent to Hong Kong to study the same epidemic as Yersin began his work on June 14 His findings and Yersin s were not the same at all points (Ref 2) and it is an interesting question whether they deserve equal credit as co-discoverers of the plague bacillus "The bacilli are to be found in the blood, in the buboes in the spleen and in all other internal organs of the victims of plague The bacilli are rods with rounded ends which are readily stained by the ordinary aniline dyes the poles being stained darker than the middle part especially in blood preparations and presenting a capsule

[1] *An interesting study of Yersin and his discovery is found in Yersin et la peste* (Lausanne F Rouges et Cie 1944) which contains articles by various authors and reprints of Yersin s own reports

were fifty broad provinces that lay in the path between them Of the men that bustled around me in the streets of Semlin there was not perhaps one who had ever gone down to look upon the stranger race which dwells under the walls of that opposite castle It is the Plague and dread of the Plague which divide the one people from the other All coming and going stands for bidden by the terrors of the yellow flag If you dare to break the laws of the quarantine you will be tried with military haste the court will scream out your sentence to you from a tribunal some fifty yards off the priest instead of whispering to you the sweet hopes of religion will console you at duelling dis tance and after that you will find *yourself carefully shot and carelessly buried* in the ground of the Lazaretto

'When all was in order for our departure we walked down to the precincts of the Quarantine Establishment and here awaited us a compromised [a com promised person is one who has been in contact with people or things sup posed to be capable of conveying infection] officer of the Austrian government who lives in a state of perpetual excommunication The boats with their com promised rowers were also in readiness

"*After coming in contact with any creature or thing belonging to the Otto man Empire* it would be impossible for us to return to the Austrian territory *without undergoing an impressment of fourteen days in the odious Lazaretto*" (chap 1)

1 VIRCHOW Rud I Ueber die Pest Berl klin Wchnschr **16** 117 1879

Virchow gives an authoritative statement of the contemporary status of plague There is emphasis as one might expect on the pathological lesions—buboes hemorrhages etc—and their significance Virchow considered the disease in fectious and contagious "*It seems to me that the resemblance of plague and* anthrax is so great that I consider it very likely that an organism will be found which is the cause of the affection [plague]" He therefore emphasized the importance of isolation of patients disinfection and quarantine The views of those who did not regard plague as contagious are brought out in the study of E H Ackerknecht, Anticontagionism between 1821 and 1867" Bull Hist Med **22**:562 1948

2 YERSIN [Alexandre] Sur la peste de Hong Kong Compt rend Acad d sc **119** 356 1894

M Duclaux communicated to the academy passages from a letter addressed to the Pasteur Institute by Dr Yersin who had been sent to Hong Kong to study plague during the great outbreak of 1894 After a brief clinical descrip tion he says The first bacteriological studies were made on living subjects Examination of the blood drawn from the finger at various stages of the disease did not show any microbes and cultures were sterile The bubos on the other hand showed in abundance and in pure state a very small bacillus short with rounded ends not staining by the method of Gram In two fatal cases the bacillus was found in the buboes and less abundantly in other glands and very rarely in the blood at the moment of death The liver and spleen were enlarged and contained the specific bacillus Mice inoculatd with a little material from a bubo died in 24 hours with the bacilli in the glands organs and blood Guinea pigs died in 3–6 days The microbe was early grown on gelatin

5 YERSIN CALMETTE and BORREL. La Peste bubonique Ann Inst Pasteur 9:589 1895

No sooner had Yersin isolated the bacillus of plague than his associates at the Pasteur Institute in Paris began immunization and protection experiments in animals A series of passages yielded organisms of "fixed" virulence "The present note had for its object to show the possibility of immunizing animals against plague and to cure those who were fatally infected by this disease" Rabbits and guinea pigs were injected with organisms heated at 58° C for 1 hour "In general 3 or 4 injections sufficed to vaccinate the rabbit against a subcutaneous injection of virulent bacilli" These workers also tried the preventive and curative action of serum of rabbits immunized against plague "3 cc of such serum sufficed to protect a rabbit against a subcutaneous injection of virulent plague bacilli This same amount of serum injected 12 hours after inoculation stops growth of the microbe and cures the rabbit of the plague" They then immunized a horse whose serum developed a marked preventive and curative action against plague in mice Normal sera or sera prepared against other bacteria had no effect These experiments from the hands of such outstanding observers attracted much attention the more so when a letter from Yersin to the academy arrived from Canton China dated June 29 1896 in which he reported the brilliant cure of a young man sick with plague by injection of "serum prepared at Nha Tsang" ("Historique du premier cas de peste traité et guéri par l'emploi de sérum anti pesteux" Bull. Acad de méd Paris 36:195 1896) Yersin's letter was accompanied by a communication from the French consul-general at Canton confirming his claims "Dr Yersin has administered serum to a Chinese Catholic gravely ill with plague Absolute success" Following the reading of this letter M Brouardel announced "A recent telegram informs me that M Yersin has already treated twenty seven cases of plague by his method with success in every case" A little later E Roux ("Sur la peste bubonique essais de traitement par le sérum antipesteux à propos d une note du Dr Yersin médecin de 2e classe des Colonies directeur de l'Institut Pasteur de Nha Tsang" Bull Acad de méd Paris 37 91 1897) reported to the academy on Yersin's work It now appeared that Yersin had treated twenty three cases of plague of which two had died Roux said that the serum was ineffective if the disease was too advanced but was very efficacious if used in the first phases In conclusion the president of the academy "thanks M Roux for his important communication and asks him to transmit to Dr Yersin congratulations and encouragement (*unanimous applause*)

Unfortunately this early enthusiasm soon had to be tempered and it would serve no purpose to attempt to review the huge literature on serum therapy N H Choksy ("On recent progress in the serum therapy of plague" Brit M J 1 1282 1908) an outstanding authority on the subject in a review of the use of various early sera reported death rates of 60–80 per cent He pointed out further that no effect was to be expected in septicemic patients In appropriate cases there was a mortality of 63 5 per cent as against 74 per cent in the controls "The whole secret of the treatment lies in applying the serum very early if given between twenty four and forty eight hours its action is not so well marked and after forty eight hours it does not appear to affect the course perceptibly" At best therefore the serum appeared of highly limited value Furthermore in reports on plague investigations in India issued by the advisory

sometimes well marked sometimes indistinct Cultural characteristics are then described Mice rats guinea pigs and rabbits were all highly susceptible to inoculation and died in from 2 to 5 days Mice and guinea pigs could be in fected by feeding Kitasato reported the effects of desiccation heat and *chemicals on the bacilli The paper concludes with "a short review of the* Plague generally Kitasato obviously regarded the disease as communicable and urged rigid cleanliness disinfection and isolation "Dead bodies covered with quicklime are either to be burned or buried Mice and rats which have died spontaneously in dwelling houses should be carried away with proper precautions Kitasato however like Yersin did not sense the true relationship between rats and plague they were unaware of the vector

4 AOYAMA T Ueber die Pestepidemie in Hong Kong im Jahre 1894 Mitt a d med Facultat d Kaiserlich Japanesichen Universitat 3 115 1897

Aoyama gives a most interesting and comprehensive report on every phase of the Hong Kong epidemic of 1894 but the most important section is that on the plague organism He notes that both Yersin and Kitasato found "specific bac teria in plague cases at about the same time but he raises the question of whether the organisms of the two workers were not different In summary "Dr Yersin has not stated that the bacilli in the blood and in the lymph nodes are morphologically different whereas Kitasato says they differ and those from the blood possess a capsule Furthermore according to Yersin the plague bacilli are Gram negative whereas Kitasato finds them sometimes positive According to Yersin after animal inoculation the regional lymph nodes are always swollen whereas Kitasato found such swelling rare" Aoyama himself *often found mixed infections and he concluded that the organisms which* Kitasato found in the blood were simply streptococci He believed that suppu ration of buboes was due to superinfection with some other organism than the bacillus of plague Ogata (Ref 7) also concluded that the organisms of Yersin and Kitasato were distinct and he listed the differences in tabular form although as distinguished a bacteriologist as W Kolle ("Zur Bakteriologie der Beulenpest" Deutsche med Wchnschr 23 146 1897) disagreed The whole question is analyzed by E Lagrange ("Concerning the discovery of the plague bacillus J Trop Med 29 299 1926)

Aoyama also gave interesting clinical observations He mentioned hyperacute (lightning like *blitzartige*) cases which died in 24 hours before buboes ap peared but he evidently did not recognize the pneumonic form He stated that he saw only one instance of pneumonia in the Chinese hospital The article con cludes with a comprehensive description of the pathological changes He em phasized especially the lesions in lymph nodes through the body and those of smaller patches of lymphoid tissue The glandular swelling consisted of "hyper aemia dilation of vessels exudate hemorrhage cellular hyperplasia and im mense bacterial growth" He described blood leukocytes of up to 200 000 The spleen was usually large otherwise no specific lesions were mentioned

An immense literature on the bacteriology of plague promptly appeared A comprehensive discussion of the plague bacillus is to be found in Pollitzer (*op cit* p 71) and in the article by Petrie (*loc cit*)

R P Strong and O Teague ("Studies on pneumonic plague and plague immunization II The method of transmission of infection in pneumonic plague and manner of spread of the disease during the epidemic" Philippine J Sc 7B:137 1912) studied in detail the transmission of pneumonic plague *Bacillus pestis* was not expelled on quiet breathing but on cough it was widely disseminated into the surrounding air even when no gross droplets of sputum were visible Strong and Teague emphasized the importance of masks and other protective measures in the presence of the pneumonic form of plague They also ("IV Portal of entry of infection and method of development of the lesions in pneumonic and primary septicemic plague experimental pathology" *ibid.* p 173) believed that the primary point of infection in pneumonic plague was not the tonsil but some part of the respiratory passages "Having reached the lung tissue the bacilli rapidly multiply and produce at first pneumonic changes of the lobular type and shortly afterward more general lobar involvement of the lung tissue"

The whole subject of pneumonic plague is exhaustively covered in the monograph of Wu Lien Teh (*A Treatise on Pneumonic Plague* [Geneva League of Nations Health Organization 1926])

7 OGATA M Ueber die Pestepidemie in Formosa Centralbl f Bakt 21:769 1897

Ogata and a group of associates were sent to Formosa to study plague He reported numerous bacteriological observations He always found the bacilli in the blood and organs of infected small animals but did not find them constantly in the blood of human cases even when severe "Fleas on plague rats contain virulent plague bacilli, which after the death of the rat can convey the plague bacillus to man" "Plague may be primarily a disease of rats and this animal may be the immediate cause of the spread of the disease in man" He therefore rated high the disposal of sick and dead rats in plague control He also stated that in Formosa the inhabitants looked on plague as primarily a pest of rats and actually designated it "rat pest" This paper seems to give the first clear statement of the transmission of plague by the rat flea A little later P L. Simond ("La Propagation de la peste" Ann Inst. Pasteur 12:625 1898) presented a beautiful epidemiological study of plague in India from which he concluded that man is of little consequence in the transmission of bubonic plague and that transmission is not by air or water "It is an animal which the observed facts denounce as the most active propagator of plague it is the rat" He went on to condemn the rat flea as the agent which transmitted plague from rat to man He pointed out the important and now well recognized fact that the death of rats preceded the death of men from plague

J Constantin Gauthier and A Raybaud (Recherches expérimentales sur le rôle des parasites du rat dans la transmission de la peste" Rev d'hyg 25:426 1903) subjected the question to experimental study and concluded "Transmission of plague by parasites is possible We have seen it take place from rat to rat by the intermediation of the fleas of this animal It does not occur by simple contact of animal with animal when all parasites are excluded from the experiment Fleas gathered from rats bite man without difficulty and this may be the cause of epidemics This study seems to us therefore a full confirmation of the theory of Simond Further proof of these early observations was re

committee appointed by the Secretary of State for India the Royal Society and the Lister Institute (The serum treatment of human plague J Hyg Vol 12, Suppl p 326 1912) it is concluded "From the whole enquiry it appears that the administration of the available sera is not a practicable means of bringing about any material diminution in the mortality from plague in India Many antiplague sera had been prepared by all sorts of methods using various animals They are enumerated in R F Platzner s review ("Evaluation of therapeutic agents in plague U S Naval M Bull 46 1674 1946) For the most part they have been variously judged by different observers in different outbreaks The whole question of serum therapy of plague is concisely reviewed by Pollitzer (*op cit* p 454) Thus the story is much the same as with antipneumococcal and antimenigococcal sera—the effect of certain sera is possibly prophylactic or curative in the treatment of mild cases at the very onset

6 CHILDE L F The pneumonic type of plague Indian M Gaz 32 231 1897

Childe working in India noted that as the epidemic progressed one observed that coincidently with the increased death rate due to plague there was a large and unexplained increase assigned to remittent fever and respiratory diseases without superficial buboes "And at the end of December I met with a case which had been diagnosed as broncho pneumonia but which turned out to be one of plague affecting the lungs without causing any marked enlargement of the lymphatic glands—a case in fact of plague pneumonia" Anatomically the lungs showed engorgement edema and pneumonic patches the lymphatic glands were little if at all enlarged the pneumonic patches showed under the microscope immense numbers of plague bacilli which were grown in pure culture Up to the time of this report Childe had made post mortem examinations on twelve such cases the patients were all brought to the hospital with no suspicion of plague The course was that of a fulminating bronchopneumonia with death in a few days the patients cough up watery seromucous fluid slightly blood tinged The physical signs were mainly those of bronchopneumonia—patches of râles Childe considered pneumonic plague as highly communicable by air borne transmission in contrast to the low contagiousness of the bubonic form With regard to the literature I have not been able to find any published account of this form of plague but it was evidently recognized during the Pali epidemic of 1836 and perhaps the 'black death of the middle ages was really a severe type of this plague pneumonia"

In 1911 the Chinese government appointed a commission (*Report of the International Plague Conference Held at Mukden April 1911* [Manila 1912]) to study a tremendous epidemic of pneumonic plague in Manchuria The commission collected evidence (p 423) that rat infection played no part in this epidemic but that the disease was spread by dissemination of bacilli by cough R P Strong working with the commission showed that the same strains of bacilli were involved in bubonic and pneumonic forms of plague and that organisms from pneumonic cases injected into animals produced the bubonic form (pp 435 438) The whole situation is summarized by W G Liston ('The epidemiological features of bubonic and pneumonic plague contrasted XVIIth Internat Cong Medicine London 1913 Sec XXI" Trop Med & Hyg Part 1 p 9 1914)

the attempt to find something more effective The subject is well reviewed with literature in Pollitzer (*op cit* p 138) Turning to recent times K F Meyer S F Quan and A Larson ("Prophylactic immunization and specific therapy of experimental pneumonic plague" Am Rev Tuberc 57 312 1948) immunized mice with avirulent strains of *B pestis* or with killed plague bacilli and found marked protection against a subsequent intranasal challenge Finally K F Meyer (*"Immunity in plague a critical consideration of some recent studies"* J Immunol 64:139 1950) gave a masterful analysis of the mechanism of infection and immunity in plague and Pollitzer (*op cit* chap 3 p 115) comprehensively reviewed with literature the subject of immunology in plague as well as (*ibid* chap 10 p 523) its control and prevention "For several years the Armed Forces [see J Love J F Shaul A Margileth and R R Martelle 'The status of immunization in 1954 M Clin North America September 1954 p 1493] have used suspensions of P pestis killed by formalin The basic course consists of 2 subcutaneous injections of 1 ml of this suspension *at 7 to 10 day intervals Each ml contains 2000 million organisms This* yields partial protection for 4 to 6 months so booster doses are advised every 4 to 6 months so long as one resides in an area where plague exists"

9 DURCK Hermann Beitrage zur pathologischen Anatomie der Pest Beitr z path Anat 6 Supplementheft p 1 *1904*

Although the classical studies on the pathology of plague are those of H Albrecht and A Ghon ("Pathologisch anatomische Untersuchungen mit Einschluss der pathologischen Histologie und Bakteriologie" Denkschriften k Akad Wissensch Wien Vol 66, Part II p 227 1898) handsomely illustrated with photographs and reproductions of microscopic preparations they are published in a rather inaccessible situation Durck also working in Bombay during the epidemic reports autopsies on sixteen cases of bubonic plague in meticulous detail both gross and microscopic with beautiful illustrative plates The pathology of plague both in experimental animals and in man is thoroughly reviewed with references to the literature by Pollitzer (*op cit* p 179) The special pathology of the pneumonic form was extensively studied in the Manchurian epidemic by R P Strong B C Lowell and O Teague ("Studies on pneumonic plague and plague immunization VII Pathology" Philippine J Sc 7B 203 1912)

10 Reports on plague investigations in India epidemiological observations in Bombay City J Hyg 7 724 1907

Outbreaks *of disease in rats were generally observed to precede outbreaks of* plague in man According to A Rennie ("The plague in the East" Brit M J 2 615 1894) "In Canton rats were the only animals observed to suffer an exceptional mortality was observed amongst them two or three weeks before cases of plague were noted and this sequence of events persisted throughout the epidemic A high mortality amongst rats in a district of the city quite free from sickness was most surely followed by an outbreak of plague so much so that people came to regard these rodents as heralds of the coming evil and when possible hastened removal to safer quarters They would come out of their holes in broad daylight run and tumble about in the streets in an aimless and dazed manner and die

ported by the British Plague Commission ("Experiments upon the transmission of plague by fleas I Historical introduction J Hyg, 6 425 1906 and II Transference of plague from rat to rat *ibid* p 435) In Part I is reviewed the literature to date and in Part II definitive experiments are described which show that plague can be transferred from rat to rat by fleas without direct contact of the animals The commission further showed (Further observations on the transmission of plague by fleas with special reference to the fate of the plague bacillus in the body of the rat flea [*P cheopis*] *ibid* 7 395 1907) that the stomach of the flea could hold 0 5 cu mm of blood that plague bacilli multiplied in the stomach and were passed out in the feces and that a flea bite could serve as portal of entry for plague bacilli A W Bacot and C J Martin ("Observations on the mechanism of the transmission of plague by fleas XVIIth Internat Cong Medicine London 1913 Sec XXI Trop med & Hyg Part II p 9, 1914) showed by ingenious experiments that rat fleas could transmit plague during the act of sucking they also studied the distribution of plague bacilli in infected fleas

The whole subject of the various insect vectors is documented in Pollitzer (*op cit* chap 7 p 315)

8 HAFFKINE W M Remarks on the plague prophylactic fluid Brit M J 1 1461 1897

Following the previous observations on vaccination with killed cultures of plague bacilli (Ref 5) the subject was taken up intensively by Haffkine at the request of the British government In this paper Haffkine gave his directions for preparing the prophylactic fluid His rationale was as follows I decided to make an atteempt to effect both a reduction of the susceptibility and of the case mortality by combining in the prophylactic substances large quantities of bodies of microbes together with intensified extracellular toxins For this purpose he added to the nutritive media large quantities of "clarified butter "When the fluid is filled with a rich jungle the growth is shaken off the drops of butter and brought down to the bottom of the liquid" The microbes were killed by a temperature of 70 C maintained for 1 hour "In a quiet position in the test tubes two different substances are then obtained a thick white sediment and a perfectly limpid fluid Injected subcutaneously into animals they produce (1) the sediment a local inflammation and a nodule at the seat of inoculation with little fever or general effect and (2) the fluid a considerable rise of temperature and a general affection with no noticeable local effects" Haffkine attributed to this mixture both prophylactic and therapeutic effects A little later editorial comment (Haffkine s plague prophylactic Brit M J 1 1492 1897) was as follows On reading the description of his [Haffkine s] technique one cannot help being struck by the roughness of the methods employed and by the wonderful success that attended them That the introduction into the body of the mixture which results from the growth of the plague bacillus in a mass chemically so complicated as a mixture of native ghee and bouillon should cause the inoculated to suffer to an extent about twenty times less than the non inoculated is indeed a remarkable fact Haffkine covered essentially the same ground in another article (The plague prophylactic" Indian M Gaz 32 201 1897) Through the years there has grown up a vast literature describing plague vaccines prepared in innumerable ways always in

for example was that of A T W Simeons ("One thousand cases of bubonic plague treated in an emergency plague hospital" Indian M Gaz 81 235 1946) He stressed the early institution of treatment with sulfadiazine when the drug was given within the first 24 hours the mortality was only 6 61 per cent whereas when its use was delayed 24 hours the death rate rose to 19 67 per cent In one thousand cases the mortality was 18 per cent The whole subject is reviewed by J M Ruegsegger and H Gilchrist ("Plague a survey of recent developments in the prevention and treatment of the disease" Am J Trop Med 27:683 1947)

14 HORNIBROOK J W Streptomycin in experimental plague Pub Health Rep 61:535 1946

Hornibrook first tested the value of streptomycin in experimental plague in mice He found a definite prophylactic and curative effect for example when treatment (2 mg per day) was started 2 days following inoculation and continued for 6 days nine out of ten mice survived for 14 days whereas 80 per cent of untreated controls died A little later N E Wayson and M C McMahon ("Plague treatment of experimental animals with streptomycin sulfadiazine and sulfapyridine" J Lab & Clin Med 31 323 1946) also showed that streptomycin had a definite therapeutic effect in mice and guinea pigs with plague The use of a combination of streptomycin and sulfadiazine did not seem to add to the effectiveness of either Denis Herbert ("Streptomycin in experimental plague" Lancet 1:626 1947) also made a thorough study of the subject He found that in guinea pigs infected by subcutaneous injection 3½-day courses of streptomycin injections (40 000 units/kg/day) gave 100 per cent survival even when administration was delayed for 48 hours after infection Streptomycin was more effective than sulfathiazole and penicillin was only slightly effective K F Meyer S F Quan and A Larson ("Prophylactic immunization and specific therapy of experimental pneumonic plague" Am Rev Tuberc 57:312 1948) also concluded that thus far the most effective therapeutic agent known for plague was streptomycin "Over 90 per cent of experimentally infected mice when in the septicemic state of lobular plague pneumonia may be cured with 5 mg of streptomycin It is recommended that human pneumonic plague be treated early in the course of the infection with daily doses of 4 to 6 gms of streptomycin and that treatment should continue for not less than six to ten days"

15 KARAMCHANDI P V and RAO K Sundar Streptomycin in human plague Lancet 1 22 1948

These writers were the first to report the use of streptomycin in human plague They described five cases all extremely ill whose temperatures promptly became normal after about 4 gm of streptomycin over a period of 36 hours A little later Ch Haddock and A Valero ("Streptomycin in bubonic plague" Brit M J 1:1026 1948) working in Haifa treated with streptomycin three patients who did not respond to sulfonamides with speedy recovery The buboes appeared to be uninfluenced if treated late and required incision and drainage C H Huang C Y Huang L W Chu and T F Huang ("Pneumonic plague" Am J Trop Med 28 361 1948) report a case of proved primary pneumonic plague in which recovery took place following continued

However there was disagreement as to the exact circumstances and their significance as brought out in a thorough review of the literature by the English Plague Commission ("Digest of recent observations on the epidemiology of plague" J Hyg 7 694 1907) The elaborate Bombay studies showed that *Mus decumanus* typically an out of door wandering rat" was chiefly responsible for the diffusion of plague among the rats throughout Bombay city and that the decumanus epizootic preceded an epizootic in *Mus rattus* which is essentially a house rat It is from the latter that the rat flea transmits the plague bacilli to man leading finally to a human epidemic

11 WHITE F Norman Twenty years of plague in India with special reference to the outbreak of 1917–18 Indian J M Research 6 190 1919

The epidemiology of plague is of great interest In this important paper White describes the situation in India where from 1898 to 1918 at least ten million people died of the disease Variations in intensity of plague outbreaks are related to rainfall variations in resistance on the part of the rat population efforts to eradicate rats etc

12 ELTON C S Plague and the regulation of numbers in wild animals J Hyg 24 138 1925

Elton gives a comprehensive summary of the occurrence of plague in wild rodents The list includes marmots in Transbaikalia marmots in the Caucasus squirrels monkeys and field mice in India gerbils and wild mice in South Africa muskrats in Senegal wild rodents in England and ground squirrels in California He concluded that most rodents regulated their numbers by increasing to a point at which some sort of epizootic such as plague occurred which killed off a large proportion of them This cycle recurred indefinitely perhaps regulated by various factors such as climatic conditions These epizootics were quite different from plague in domestic rats and it has been a question whether human plague results from them Wu Lien Teh ("A further note on natural and experimental plague in tarbagans" J Hyg 22 329 1924) considered it "as practically certain that the tarbagan give rise to the outbreaks of plague which occur yearly in Transbaikalia and that it started the outbreaks in Manchuria in 1910–11 and 1920–21" Plague among the ground squirrels of California was first reported by G W McCoy ("Plague among ground squirrels" Am J Hyg 10 589 1910) as well as a few human cases from this source Karl F Meyer ("The Sylvatic Plague Committee Am J Pub Health 36 961 1936) takes up the problem of the Sylvatic plague in California and the whole subject of hosts of the infection is exhaustively dealt with in Pollitzer (*op cit* chap 6 p 251)

13 CARMAN John A Prontosil in the treatment of oriental plague East African M J 14 362 1938

Carman seems to have been the first to use a sulfonamide in the treatment of plague In a small series the death rate was 50 per cent as against 100 per cent in the controls H Schutze ("Chemotherapy in plague infection" Lancet 1 266 1939) shortly after reported various sulfonamide derivatives as effective in experimental plague of rats and mice From then on the journals contained many reports of the use of sulfonamides in plague An important paper

BRUCELLA INFECTION

Bacteriology	Refs 2 3 4 9 13 14 15 19 27 29
Blood in	Ref 36
Cattle relation to brucellosis	Refs 9 31
Chronic or ambulatory form	Refs 8 17
Clinical	Refs 1 2 3 4 5 8 10 20 22 31
Diagnosis	Ref 44
Epidemiology	Ref 20
General	Refs 1 2 3 4 6 12
Goats relation to Malta fever	Refs 16 18
Immunology	Refs 11 25 26 28
Mode of infection	Refs 21 23 32
Pathology	Refs 24 30 34 43
Serum diagnosis	Refs 7 8 26
Treatment	Refs 35 37 38 39 40 41 42

therapy with sulfonamides and streptomycin P Wagle ("Recent advances in the treatment of bubonic plague Indian J M Sc 2 489 1948) also found streptomycin the most effective drug In cases with heavy blood stream inva sion the mortality of patients treated with serum was 100 per cent with sulfa diazine 50 per cent and with streptomycin 27 2 per cent From this time on numerous confirmatory papers appeared K F Meyer (Modern therapy of plague" J A M A 144 982 1950) summarized the whole matter of therapy Streptomycin is advised as the agent of choice to be supplemented in very severe cases by oral use of aureomycin chloramphenicol or terramycin as well as antiplague immune serum globulin If antibiotics are not available the sul fonamides (sulfadiazine or sulfamerazine) are advised

16 SOKHEY S S and HABBU, M K Aureomycin and chloromycetin in the treatment of experimental plague Indian J M Research 38 197 1950

The writers found both these antibiotics highly effective in experimental plague in mice Even when given after septicemia had developed a suitable dose saved almost all the animals These drugs had the advantage over streptomycin in being effective when given by mouth and this was the first report on their use in plague A little later K. Ramachandran ("Treatment of plague with aureo mycin J Indian M A 21 217 1952) cured thirteen of fifteen cases of bu bonic and septicemic plague by use of aureomycin F R McCrumb and others (Chloramphenicol and terramycin in the treatment of pneumonic plague Am J Med 14 284 1953) found in pneumonic plague that either chloram phenicol terramycin or streptomycin produced dramatic clinical response in those patients receiving therapy prior to the twentieth hour

In summary then the position as to therapy seems at present (1957) as follows "Immune sera have had a checkered career for many years None of them seems very effective Perhaps used very early they have slight protective and antitoxic effects in mild cases Sulfonamides especially sulfadiazine have a definite therapeutic effect especially when used early in mild cases The antibiotics—streptomycin aureomycin terramycin and chloramphenicol—seem by far the most potent weapons since they have cured advanced septicemic and pneumonic cases The question of modern therapy is discussed and docu mented by Pollitzer (*op cit* chap 8 p 409 "Clinical aspects")

17 ONESTI Silvio J Plague press and politics Stanford M Bull 13 1 1955

It has happened repeatedly that public officials have refused to acknowledge the presence of plague when the disease had obviously appeared in their midst Such was the case in San Francisco in the outbreak of 1900 The story of this incident is vividly told and fully documented by Onesti "The account of the bubonic plague in San Francisco is one of the darkest pages in the history of North American medicine "

bronchitis or diarrhoea as a rule The patient is prone to relapses and the disorder is followed by a protracted convalescence and chloroanaemic aspect very frequently also by rheumatism of some form or other but without any tendency to lesion of the peri or endocardial membranes Pathologically it is marked by congestion or inflammation with softening of the enteric mucous membrane without any lesion of Peyerian follicles but with hypertrophies of liver and spleen. There is no fever so irregular as this in its course and symptoms Convalescent stage It is now that the anaemic but puffy looking face and the dejaded [*sic*] look attract attention Supposing that no relapses occur the patient rarely recovers perfectly without suffering from rheumatism or some form of neuralgia" The cause of the disease Marston guessed to be filth and poor sanitation

However there was no clear general recognition of the disease until Bruce (Ref 2) isolated the causal organism as is shown by the confusion displayed in contemporary accounts (G F Duffey "On rheumatic orchitis as a sequel to fever" Dublin J M Sc 53:97 1872 W C McLean "On Malta Fever with a suggestion" Brit M J 2:224 1875 O G Wood "Malta fever" Edinburgh M J 22:40 1876 J Lane Notter "On Malta fever" Edinburgh M J 22:289 1876)

2. BRUCE David Note on the discovery of a micro-organism in Malta fever Practitioner 39:161 1887

Bruce working in the army at the Station Hospital at Valletta Malta began his paper as follows "This fever has a wide distribution in the Mediterranean It is identical with the Rock fever of Gibraltar the Neapolitan fever of Naples the Country fever of Constantinople and the New fever of Crete On further investigation I have no doubt this list could be much enlarged " Although a good deal has been written on the clinical aspects "there is as far as I am aware no notice regarding the presence of micro-organisms in the organs of fatal cases"

Bruce next sketched the clinical features "It is a disease of long duration ninety-one cases having an average stay in hospital of 85 5 days The fever which often runs high is continued remittent and intermittent in type An undulatory type of curve is frequently observed the undulations being separated by a period of apyrexia Sometimes these undulations persist for a long time in one case I observed two well marked waves between the 120th and 160th days of the disease" Bruce also emphasized enlarged spleen sweats constipation bronchitis pains swelling of joints and orchitis "The mortality is as a rule exceedingly small"

Five fatal cases were examined for micro-organisms the first by means of stained sections the remaining four by inoculation into tubes containing agar agar nutrient jelly In the first case sections of spleen stained by Gram s method and also with methylene blue showed enormous numbers of single micrococci scattered through the tissues Bruce next inoculated blood from severe cases obtained by puncturing the fingertip into tubes of agar they remained sterile except for two which were obviously contaminated Bits of spleen were also inoculated into the tubes Growth was slow but it appeared in all the tubes placed in the incubator at 37 C after a period of 68 hours "The growth appeared at first as minute pearly white spots scattered around the point of

Section 5

BRUCELLA INFECTION

THE book by Surgeon Captain Louis Hughes (Ref 6) is generally accepted as the storehouse of information on the early knowledge of Malta fever I F Huddleson s monograph *Brucellosis in Man and Animals* (New York Commonwealth Fund 1943) contains much useful general as well as bacteriological information and has a comprehensive bibliography The monograph by H J Harris *Brucellosis (Undulant Fever) Clinical and Subclinical* (2d ed New York Paul B Hoeber 1950) is also to be mentioned This volume of some six hundred pages deals with every phase of the subject under the heading of "Symptomatology for example all the rare clinical phenomena of brucellosis such as endocarditis ocular troubles intermittent hydrarthrosis and others are described with references to the literature However the recent authoritative work of W W Spink *The Nature of Brucellosis* (Minneapolis University of Minnesota Press 1956) with bibliography of some nine hundred titles supersedes all previous books on the disease With regard to the bacteriology of brucello is the article by J T Duncan L E H Whitby and A D McEwen in *A System of Bacteriology in Relation to Medicine* (London H M Stationery Office 1930) ch ix p 386) is authoritative and comprehensive as is the section in Topley and Wilson s *Principles of Bacteriology and Immunity* (3d ed Baltimore Williams & Wilkins Co 1946) 2 1692 As to general bibliographies Hughes s book contains a comprehensive list of references to the early literature (Ref 6 p 29) and is supplemented by a compilation of publications from 1897 to 1907 by J W H Eyre in the British Commission *Reports* (Ref 12) Part V (1907) p 66

1 MARSTON J A Report on fever (Malta) Army Medical Department Statistical Sanitary and Medical Reports for the Year 1861 p 486 London Harrison & Sons 1863

Although it is probable that Malta fever" had existed for a long time in the Mediterranean Basin the early accounts of fevers in this location were too confused for intelligent classification [1] Marston discussed the fevers seen at Malta and after separating typhoid and some others gives we believe the first recognizable account of Malta fever under the designation of Mediterranean remittent" "By this is meant a fever characterized by the following symptoms and course A preliminary stage of subacute dyspepsia anorexia nausea headaches feeling of weakness lassitude and inaptitude for exertion mental or physical chills muscular pains lastly a fever having a very long course—three to five or ten weeks—marked by irregular exacerbations and remissions great derangement of the assimilative organs tenderness in epigastric region splenic enlargement slight jaundice without any exanthem Neither

[1] The book by William Burnett (*A Practical Account of the Mediterranean Fever as It Appeared in the Ships and Hospitals of His Majesty s Fleet on That Station With Cases and Dissections* [London J Callow 1816]) is mentioned as giving an early account of Malta fever but one searches through it in vain for anything that can be recognized as the disease in question

food and when required by stimulants and by attention to ordinary hygienic principles Removal of the patient from the infective area does not cut short the course of the fever "

Bruce knew nothing of the chronic low grade forms of infection he thought of the disease as analogous to typhoid In these papers there is also no mention of goats or any implication that they are concerned with the disease The mode of entry of the organism was a complete mystery

In still another paper ("Notes on Mediterranean or Malta fever I Its bacteriology" Brit M J 2:58 1893) Bruce added still more observations all confirmatory He produced the disease in several monkeys from which he again recovered the organism which he now called *Micrococcus melitensis* A beautiful *undulating temperature chart from Monkey VI is reproduced extending* over a period of 98 days The bacteriologic features are redescribed and Bruce now states that the organism is Gram negative

4 HUGHES Louis Investigations into the etiology of Mediterranean fevers Lancet 2:1265 1892

A G P Gipps ("On Malta fever" Tr Epidemiol Soc London N S 9:76 1891) isolated an organism similar to that of Bruce from two cases of Malta fever but Hughes's work also done in Malta was much more extensive Hughes again described the disease "Clinically it has a peculiarly irregular temperature curve consisting of intermittent waves of pyrexia of a distinctly remittent type each wave lasting from one to three weeks with generally an apyrexial interval of two or three days This pyrexial condition is usually very chronic, lasting even six months or more and is not markedly affected by quinine or arsenic It is usually accompanied by obstinate constipation progressive anemia and debility and is followed in a large number of cases by very chronic neuralgic and rheumatic complications from which the patient may not recover for perhaps two years The death rate is very low but as the average stay in hospital is 70 to 90 days the expense incurred by the State has reached an enormous sum " Hughes recovered the organism from the spleens of five fatal cases he carried it through six generations of pure culture In two cases it was demonstrable microscopically in fresh splenic substance The organism was not found in other disorders such as enteric fever Hughes produced the disease in series in monkeys He gave a detailed description of the organism and its cultural characteristics He emphasized the slow growing delicate character of its growth on the available media He concluded that the presence of the organism was connected with human excrement but he also believed "that the poison of this fever when infecting the human body is aerial in nature and that in most cases it enters the human frame by way of the air passages" No mention was made of goats

It is of interest that both Bruce and Hughes were so imbued with the current theories of miasms that they were reluctant to give up the idea of air borne infection even though they had produced Malta fever in monkeys by subcutaneous injection

"This morn we came near Malta, or as twas called formerly Melita from the abundance of honey they have there gathered by the bees from the aniseeds and flowers thereof which grow on this island abundantly (*The Diary of Henry Teonge Chaplain on Board H M s Ships Assistance British and Royal Oak 1675–1679* [New York Harper & Bros 1927])

puncture Small round colonies could be seen along the needle track exam ined under a high power innumerable small *micrococci are seen" Similar find* ings were obtained in three other fatal cases "From a consideration of the above facts I think it will appear *to be sufficiently proved (a) that there exists* in the spleen of cases of Malta fever a definite micro-organism and (b) that this micro organism can be *cultivated outside of the human body* I have already cultivated four successive generations It remains now to be seen what effect if any *this micro organism has on healthy animals where it is to be* found how it gains entrance to its human host and many other points" Curiously enough *Bruce did not state whether the organism was Gram positive* or negative He did emphasize the absence of intestinal lesions thus eliminat ing confusion with "enteric fever

In a second paper ("The micrococcus of Malta fever" *ibid* 40 241 1888) Bruce obtained the same organism from another fatal *case and described* it more in detail It is oval in form and measures from 0008 millimetres to 001 millimetres *In sections they are seen to* be scattered singly or in pairs throughout the substance of the tissue and never occur in masses" "One fact to be noted is the rapidity with which *the micrococci* became wholly unstained by the addition of absolute alcohol The organism showed no sign of growth at a temperature below 22 C Bruce gave a frequency curve of case incidence most cases occurred during May–August but some were encountered even in winter Bruce injected some culture into a monkeys arm after a severe febrile illness the animal died and the organism was recovered from spleen and liver Small animals on the whole gave negative or doubtful results on inoculation

3 BRUCE David Observations on Malta fever Brit M J 1 1101 1889

Bruce no longer in Malta but now assistant professor of pathology at the Royal Victoria Hospital Netley writes a masterful systematic article on Malta fever He begins with "Definition An endemic disease of long duration characterized by fever continuous remittent and intermittent in type in most cases enlarged spleen profuse perspiration sudamina constipation relapses almost invariably accompanied by pains of a rheumatic or neuralgic character sometimes swelling of joints or orchitis ending almost always in complete recovery in fatal cases enlargement and softening of spleen congestion of the duodenum and upper part of jejunum no swelling or ulceration of Peyer s glands and the constant occurrence in various organs of a species of micrococcus These various features are next analyzed in detail the prevalent view that this like many other fevers was due to sewage "bad air or bad smells is discussed Bruce points out that young adults are most frequently *affected that Malta fever* alternates *with* enteric fever from which and from malaria it must be differentiated that *whether or not* one attack *conveys immunity is uncertain The details* of symp toms are analyzed in brilliant fashion as the differential diagnosis is discussed *As to pathologic* changes Bruce describes as the principal lesion proliferation of endothelial cells in lymph nodes spleen and other organs together with congestion cloudy swelling and in certain situations infiltration of small round cells The lesions of typhoid and malaria are definitely absent He concludes 1 Malta fever is a specific disease 2 It is caused by the entrance into the system of a minute parasite 3 No drug at present known has any power of modifying the action of the bacteria in the system 4 Treatment is to be princi pally directed to keeping up the patient s strength by fluid easily digested

neither enlarged nor ulcerated nor is ulceration present in other parts of the small intestine There is a constant occurrence in certain tissues of a definite species of micro-organism" (p 1) He insisted that undulant fever was a specific disease to be clearly distinguished from typhoid fever and malaria he discussed the differential diagnosis in detail He gave arguments in favor of the name he had suggested—undulant fever Then comes a historical sketch of the disease of the greatest value followed by an invaluable bibliography through 1897 giving many references not to be found anywhere else The next chapter deals with a description of the organism and the results of animal inoculation As to predisposing causes Hughes went wrong like all before him and vaguely blamed the disease on lack of sanitation which certainly was outstanding in Malta at the time and is graphically described Goats are not mentioned any where in the book. While the disease occurred throughout the year most cases were in July August and September Apparently one attack conferred im munity Hughes distinguished malignant cases—very severe although rarely fatal, the undulatory type ("finally the patient is reduced to an emaciated anaemic and bed ridden condition") an intermittent type and irregular and mixed types *There is a brilliant section on symptoms—with illustrative tempera* ture curves—in which every phase of the clinical features is analyzed The over all mortality was about 2 per cent. The gross morbid changes at autopsy were not very striking the spleen was invariably enlarged and congested Micro-scopically the appearances "are not in any way specially characteristic of un *dulant fever but rather those of severe and prolonged pyrexia acting on the tis* sues of the body" Neither Hughes nor Bruce apparently found the specific lesion described later (Refs 24 30) As to treatment "There is no drug of a specific nature at present known which will cut short an attack of the fever by its action on the virus as does quinine in ague and mercury in syphilis"

7 WRIGHT A E and SMITH F On the application of the serum test to the differential diagnosis of typhoid and Malta fever Lancet 1 656 1897

Wright, who was an early pioneer in serodiagnosis of infections described the technique of his method Serum from the patient was mixed with young cul tures of various bacteria in capillary tubes A positive test was indicated by macroscopic clumping Wright was able by means of this test, to differentiate clinically doubtful cases of Malta fever and typhoid fever In another paper (A. E Wright and D Semple "On the employment of dead bacteria in the serum diagnosis of typhoid and Malta fever" Brit M J 1 1214 1897) the use of dead cultures was introduced and found to give just as definite results as live organisms Wright and Semple spoke of the advantages of this method to the general practitioner "It will obviously be possible for every medical man to *obtain a supply of capsules of dead typhoid and Malta fever bacteria for serum* diagnosis from a central laboratory He will be able to carry about these cul tures without risk

8 MUSSER J H and SAILER Joseph A case of Malta fever Philadelphia M J 2 1408 1898

The writers report a typical case of "Malta fever" in an army officer who had probably contracted the disease in Puerto Rico A characteristic chart of pro-longed undulating fever is shown and the patient s serum agglutinated a cul ture of Bruce s organism in a dilution of about 1 50 In "Further notes on a case

Both Bruce (Sur une nouvelle forme de fievre rencontré sur les bords de la Méditerranée Ann Inst Pasteur 7 289 1893) and Hughes (Sur une forme de fièvre fréquent sur les côtes de la Méditerranée *Ann Inst Pasteur* 7 628 1893) wrote systematic articles on the disease in 1893 using mainly their old material Hughes concluded his paper in rather confused fashion It appears to be a contagious fever of a mobile type [*d'un type mobile*] characterized by an indefinite duration and an irregular course caused by a poisoning of the blood *of fecal origin and capable of assuming an aerial organized form" Bruce on* the other hand was more clear I believe I have shown that the *Micrococcus melitensis* is the cause of Mediterranean fever and that this is an absolutely specific disease distinct from typhoid and malaria As to the important question of the mode of entry of the parasite into man whether by air water or food one *does not know yet and the difficulty in growing the organism is an obstacle in* answering this question

5 HUGHES M Louis Undulant (Malta) fever Lancet 2 238 1896

Hughes first gives an immense list of the names which have been applied to the disease and after criticizing them suggests the designation "undulant fever" It has occurred to me that the term Undulant Fever by referring to the peculiar pyrexial curve so characteristic of the disease might prove a serviceable name The name appeals forcibly to the clinical observer who standing in a ward surrounded by cases of this fever (as anyone may do in summer in any of the military hospitals of Malta) gazes at the *temperature charts on the walls* and notices the way in which the recorded pyrexial curves undulate across the paper in waves of varying degree

6 HUGHES M Louis Mediterranean Malta or undulant fever London Macmillan & Co 1897

This book is a landmark in the history of the subject as Hughes summarized in authoritative fashion all that was known to date about the disease "When the writer arrived in Malta towards the end of the year 1890 for a six year tour of service in that place he found that his medical work would chiefly consist dur*ing the greater part of the year of treating a fever about which no two medical* officers appeared to agree respecting its cause treatment or even name Some even doubted its specific nature calling it a variety of enteric or malarial fever and until the writer had been present at a post mortem examination on a fatal case he was himself prejudiced in favour of all serious cases being of an enteric [typhoid] nature The fallacy of this theory soon became apparent and extended clinical and pathological experience showed how much there was to *learn and how little to guide anyone in the study of this important fever*" Hughes himself acquired Malta fever and learned first hand about it (Preface) He gave the following definition of the disease on which he elaborated at length "An endemic pyrexial disease occasionally prevailing as an epidemic having a long and indefinite duration an irregular course with an almost invariable tendency to undulatory pyrexial relapses It is usually characterized by constipation profuse perspirations and accompanied or followed by symptoms of a neuralgic character Often accompanied by swelling and effusion of the joints and other rheumatoid symptoms After death the spleen is found to be enlarged and often softened *many of the organs congested but Peyer's glands*

definite zone about 0 5 cm under the surface and 1–1 5 cm thick No colonies grew above or below this zone which indicated that the organism was sensitive to oxygen tension The colonies were small and round and consisted of small bacilli of the same appearance as those found in the uterine exudate Further cultural characteristics are given Bang soon obtained material from twenty-one cases of contagious abortion and the "*Abortusbacilli*" were found in practically all In two experiments in which a pure culture of the bacillus was introduced into the vagina of the cow abortion followed "By these two observations we have brought full proof that the organisms discovered by us are the cause of epidemic abortion" "We have had no opportunity to experiment with goats" but a colleague saw a goat abort living in a stable where cows had previously aborted. This makes it highly likely that our bacillus is also infectious for goats" Here then is the first hint of a relation between Malta fever of goats and contagious abortion of cattle

Bang s work was soon confirmed by Hugo Preisz ("Der Bacillus des seuchenhaften Verwerfens" Centralbl f Bakt 33:190 1903) and subsequently by many other workers

10 BIRT C and LAMB G Mediterranean or Malta fever Lancet 2 701 1899

Final direct proof of the causal role of *M melitensis* in Malta fever was brought by laboratory infections two of which were reported by these authors In one case a man accidentally scratched himself with the needle of a syringe with which he had just injected living growth into a horse Fifteen days later he went through a typical attack of Malta fever In a second case a man injected a small amount of agar culture into his arm Sixteen days later symptoms set in and he pursued a characteristic course K F Meyer and B Eddie (Laboratory infections due to Brucella " J Infect Dis 68 24 1941) later reported and analyzed "74 histories of brucellosis observed among bacteriologists pathologists and other workers who in the course of their duties were exposed to Brucella in the laboratories of the United States" They adduced evidence that "injections with dead vaccines fail to prevent laboratory infections

11 LEISHMAN W B Some experiments in connection with "stimulins" Tr Path Soc London 56 341 1905

Leishman working in the early days of studies on phagocytosis and opsonins ("stimulins) showed that ingestion of *M melitensis* by leukocytes was tremendously increased by adding a little Malta fever convalescent serum to the mixture The average number of germs phagocyted by each polynuclear was increased for example from 17 6 to 70 I F Huddleson H W Johnson and E E Hamann (A study of the opsono-cytophagic power of the blood and allergic skin reaction in Brucella infection and immunity in man" Am J Pub Health 23:917 1933) later elaborated and laid stress on this test along with a skin test as an indication of infection with Brucella Infection in an individual is indicated by a positive allergic skin test obtained with Brucella nucleoprotein in conjunction with negative or low opsono-cytophagic activity of the whole citrated blood for Brucella" The value of this test has been variously judged by others (Ref 44)

of Malta fever a study in serum diagnosis *ibid* 4 89 1899 they give a follow up report on this patient whose fever dragged along and whose serum repeatedly agglutinated *Micrococcus melitensis* but gave no Widal reaction for typhoid

This is claimed to be the first case reported in the Western Hemisphere[3] Charles F Craig ("The symptomatology and diagnosis of Malta fever with the report of additional cases" Internat Clin 4 89 15th Ser 1906) described instances from the army including one of a nurse who had never been out of the country apparently the first recorded indigenous case Her serum agglutinated the organism in a dilution of 1 250 Craig also referred to chronic cases In many cases of Malta fever however, after the initial attack a chronic infection results and is characterized by symptoms so slight as to be almost unrecognizable unless watched for and understood He pointed out that this form of the disease was often confused with chronic arthritis and muscular rheumatism and he reported examples Malaria typhoid fever tuberculosis pneumonia septicemia relapsing fever Hodgkin s disease and articular rheumatism are to be considered in the differential diagnosis He also emphasized the lack of pathognomonic symptoms postulated a wide unrecognized distribution of the disease and the importance of applying the serum test" in all undetermined cases of fever in all regions Thus Craig definitely widened the concept of the disease from that of the early writers (see also Ref 17)

9 BANG B Die Aetiologie des seuchenhaften (infectiosen) Ververfens Ztschr f Thiermed 1 241 1897

Abortion of cattle had long been considered contagious J Penberthy ("Enzootic abortion J Comp Path & Therap 8 100 1895) quoted a statement in the *Complete Farmer* for 1807 as follows "It is considered certainly contagious and when it happens the abortion should be immediately buried and the cow kept as widely apart as possible from the herd As the bacteriologic era developed it was inevitable that an infectious agent should be sought Nocard for example ("Recherches sur l avortement épizootique des vaches" Rec de méd vét 3 669 1886) made cultures from the puriform material laid down between the uterus and ovum and isolated two types of bacteria—micrococci and short thick bacilli Although he was not able to grow them in pure culture it is highly probable that the "micrococci" were identical with *B abortus* Bang was able to obtain the generative organs fresh from a cow in which abortion was threatened Cultures were made within 6 hours of death When the uterus was opened under aseptic conditions we saw between the mucosa and the egg an abundant non odorous exudate the examination of cover glass preparations of this material stained with methylene blue (Loeffler) immediately disclosed the presence of very small bacteria apparently in pure culture Infectious abortion is to be considered as the consequence of a specific uterine catarrh caused by a special bacterium" Bang was able to grow the organism in pure culture in deep tubes of serum gelatin agar in which colonies appeared in a

[3] The cases of J M Da Costa ("Protracted continued fever" Am J M Sc 3 629 1896) sometimes mentioned in the literature as being instances of brucellosis are too indefinite to allow any conclusions Such cases at the time were often called typhoid malaria the designation used in the first run of the Surgeon General s catalogue

and water for 20 minutes swabbing with ether for 10 minutes and finally scrubbing with perchloride of mercury for ½ hour "A sterile dressing should then be applied soaked in the same disinfectant until the time of the operation [the venipuncture] about 24 hours afterwards" E A Shaw ("Interim report of experimental work etc" British Commission Part I p 95 1905) summarized the work of the commission to date and pointed out with reference to blood culture that the organism existed in the circulation "in relatively very small amount" that it might be isolated at any stage of the disease as early as the 7th day as late as the 98th and even after the temperature had been normal for several days as in Keefer's case (Ref 31) and that there was no regular relation between the number of organisms in the blood and its agglutinating power In a still later paper Shaw ("On the quantitative bacteriological examination of the blood of 103 Mediterranean fever patients" British Commission Part III p 5 1905) reported isolation of the organism in about two-thirds of the patients "M melitensis exists in the blood in relatively small amount not having been found in association with a less quantity of blood than 4 cu mm and that only in two cases out of 103"

16 HORROCKS W H Preliminary note on goats as a means of propagation of Mediterranean fever Proc Roy Soc London 76 378 1905

Horrocks wished to ascertain by experimental inoculation whether goats could be infected by *M melitensis* Preliminary examination of the animals showed however that their serum agglutinated the organism in dilutions up to 1 300 and that cultures of milk even when the goat appeared well often yielded *M melitensis* Horrocks concluded "The results obtained show that some of the goats in every herd examined are suffering from Mediterranean fever The M melitensis is exuded in the milk in enormous numbers when the disease has been present sufficiently long He also isolated the organism from the urine of goats "when the disease has existed for some time"

Associated in this work with Horrocks was Dr T Zammit, who actually carried out the first agglutination tests with the sera of six goats ("A preliminary note on the examination of the blood of goats suffering from Mediterranean fever" British Commission Part III p 83 1905) This was the first proof that goats were of importance in the transmission of Malta fever Horrocks with J C Kennedy ("Goats as a means of propagation of Mediterranean fever" British Commission Part IV p 37 1906) later elaborated his early studies He found that 41 per cent of the goats in Malta were infected judged by the serum reaction and that 10 per cent of the goats supplying milk appeared to excrete *M melitensis* often with no change in the physical characteristics of the milk and without the animals exhibiting signs of ill health Excretion was often intermittent Monkeys and goats were infected by feeding cultures or by feeding infected milk with an incubation period of 3–4 weeks Goats also became infected by feeding on dust polluted with urine from patients Finally Horrocks found that pasteurization (68 C for 10 minutes) destroyed the *M melitensis* in infected goat s milk

17 SHAW E A The ambulatory type of case in Mediterranean or Malta fever British Commission Part IV p 8 1906

Shaw examined the blood of 525 dockyard workers all apparently healthy Among these a markedly positive reaction was given by the blood serum in 22

12 Reports of the Commission appointed by the Admiralty the War Office and the Civil Government of Malta for the investigation of Mediterranean fever under the supervision of an Advisory Committee of the Royal Society Parts I–VII London Harrison & Sons 1905–7

"The Mediterranean Fever Commission had its origin in a letter from Mr Secretary Lyttleton dated January 25 1904 addressed to the Royal Society in which he states that his attention has recently been called to the prevalence of Mediterranean fever in Malta among the Naval and Military forces as well as the civil population

"It accordingly appeared to him to be desirable that the investigation of this fever should be taken in hand and he addressed a despatch to the Governor of Malta proposing the appointment of a joint Commission representing the Army the Navy and the Civil Government

The Royal Society nominated a committee to direct the investigations which were published in seven parts over a period of three years Every phase of the subject was studied—bacteriology epidemiology relation of the disease to goats transmission to animals and clinical features In the final section practical recommendations for controlling Malta fever were made The commission did monumental work and really skimmed the cream in the study of the disease

In subsequent sections we shall mention some of the most important individual studies they will be listed under the heading British Commission"

13 HORROCKS W H Further *studies on the saprophytic existence of* Micrococcus melitensis British Commission Part I p 14 1905

The author concluded "1 The M melitensis retains its vitality in sterilized tap water for 37 days 2 In a Maltese soil allowed to dry naturally the M melitensis survives 43 days 3 The M melitensis survives for 72 days in a damp soil 4 Exposure to the sun for a few hours kills the M melitensis 5 The M melitensis survives for 25 days in sterilized sea water"

14 HORROCKS W H On the recovery of the Micrococcus melitensis from the urine faeces and sweat of patients suffering from Mediterranean fever British *Commission* Part I p 21 1905

Horrocks isolated the organism from the urine of *many patients from* the fifteenth *to the eighty second day of disease* he was unable to isolate it from feces or sweat J Crawford Kennedy (On the recovery of Micrococcus melitensis from the urine of Mediterranean fever patients British Commission Part III p 56 1905) recovered the organism from 186 of 1 974 samples of urine examined He found that excretion would appear to be of two kinds (1) an enormous *sudden gush or (2) a long continued excretion of small quantities* Bacteremia continued in some cases after the patients had been discharged as clinically well

15 GILMOUR R T Description of a method of cultivating the Micro*coccus melitensis from small quantities of* peripheral blood and inoculation experiments with the micro organisms isolated British Commission Part I p 73 1905

Gilmour drew blood by venipuncture and succeeded in isolating *M melitensis* in broth culture It is of interest that *preparation for the procedure consisted of* shaving the arm scrubbing with brush and carbolic soap with sterile nail brush

A more complete history of this outbreak is given by I H A Clayton (British Commission Part VII p 107 1907)

Among the conclusions of this report were the following The most common method of acquiring the disease is by the ingestion of infected articles of food—mainly milk The next common path of infection is by subcutaneous inoculation (see also Ref 32) during the handling of contaminated material—usually milk *Micrococcus melitensis* is not destroyed during the process incident upon the manufacture of the ordinary ice creams or of the native cheeses and it may be present in the retail articles living and unaltered in virulence

As a result of these studies the writers drew up "Recommendations as to preventive measures in connection with Mediterranean fever in Malta" of which the main points were the control of infected animals and the elimination of infection in foodstuffs

22 FERENBAUGH Thomas L. Endemic Mediterranean fever (Malta fever) in Southwest Texas" J A M A 57 730 1911

Ferenbaugh first suspected that the "goat fever" which occurred in young men working in a "goat camp" in the Pecos River country was really Malta fever He reported four patients with indeterminate prolonged fever whose sera all gave positive agglutination tests with *M melitensis* In a second paper with Gentry (E R Gentry and T L. Ferenbaugh "Endemic Malta [Mediterranean] fever in Texas with the isolation of the Micrococcus melitensis from two patients" J A M.A 57:889 1911) he isolated the organism in broth cultures from two more patients In a third paper Gentry and Ferenbaugh (Endemic Malta [Mediterranean] fever in Texas" *ibid* p 1045) made an epidemiologic study in which they demonstrated infection by means of agglutination tests in 34 per cent of the goats examined "All cases of Malta fever found have occurred in territory devoted to goat raising and all patients either gave a history of drinking unboiled goat s milk or were actively connected with the goat raising industry" Finally in a fourth paper (Malta fever in Texas" *ibid* p 1127) Gentry and Ferenbaugh reported more extensive observations on infection among the bands of goats of which there were approximately 175 000 raised for the mohair which they produced They suggested that infection arose from dust as well as from drinking milk These studies were of great importance because they demonstrated endemic infection in a goat raising area in the United States quite analogous to the situation in Malta

23 SCHROEDER E C and COTTON W E H The bacillus of infectious abortion found in milk Twenty-eighth Annual Report of the Bureau of Animal Industry U S Department of Agriculture Washington p 139 1911

During routine tests for tubercle bacilli in milk by means of guinea pig inoculation curious lesions (see Ref 24) resembling tuberculosis but lacking acid fast bacilli were encountered in some animals The disease was transmissible from guinea pig to guinea pig Milk from perfectly healthy cows tuberculin negative sometimes produced these lesions A small organism identified as *Bacillus abortus* was found in the milk which caused the disease resembling tuberculosis There is a detailed description and good pictures of the lesions in the guinea pig which correspond to those described by Smith and Fabyan (Ref 24) The striking thing in this study was the frequent occurrence of *B abortus*

cases On taking the temperatures several had slight elevations of over 99 From 3 of these cases *M melitensis* was recovered from both blood and urine from 1 it was obtained from the blood only and from 6 from the urine only The author concluded that the existence of ambulatory cases previously uncertain is now proved (see also Craig Ref 8)

Observations of this sort have been repeatedly made throughout the years as for example by Parker Dooley (Undulant fever an epidemic of subclinical infection with Brucella " Arch Int Med 50 373 1932) who found that in a group of 263 persons using infected raw milk 41 per cent were found to have serum agglutinins against *Brucella abortus* and 2 had clinical undulant fever

This phase of the subject has recently been subjected to penetrating analysis by W W Spink (What is chronic brucellosis? Ann Int Med 35 358 1951) He discusses the vague entity often diagnosed as chronic brucellosis and sets up criteria which justify a positive diagnosis

18 SHAW E A Mediterranean fever in goats cows and other animals British Commission Part IV p 16 1906

Shaw infected goats experimentally and also studied the incidence of natural infection Of 96 goats in full milk 30 were found to have sera which agglutinated *M melitensis* Organisms were recovered from the milk in 9 of these and their infectivity was demonstrated on a monkey Shaw thought that the most likely route of infection was via the gastrointestinal tract It is of great interest that he found 10 of 33 cows infected *M melitensis* was recovered from the milk of 2 of them No relation was sensed however between these findings and those of Bang (Ref 9)

19 KENNEDY J Crawford Bacteriological examination of cases of Mediterranean fever British Commission Part IV p 92 1906

In post mortem material *M melitensis* was frequently recovered from spleen liver kidney lymph nodes bone marrow and bile but never from intestines salivary glands tonsils pleural or cerebrospinal fluid

20 DAVIES A M Report on the prevalence of Mediterranean fever amongst British troops in Malta 1905 British Commission Part IV p 105 1906

It is of interest that at the end of this elaborate study the writer concluded that water and milk had nothing to do with transmission but that infection most likely occurred by direct or semi direct contagion or through the agency of mosquitos

21 EYRE J W H McNAUGHT J G KENNEDY J C and ZAMMIT T Report upon the bacteriological and experimental investigations during the summer of 1906 British Commission Part VI p 3 1907

This report contains among other interesting material an account of the famous incident of the outbreak of Mediterranean fever on board the S S "Joshua Nicholson which was transporting 61 milch goats from Malta to Antwerp where they were transferred to the S S "St Andrew" bound for New York During the voyage the personnel of the ship drank largely of goat s milk and a considerable number acquired Malta fever Thus there was carried out an "unpremeditated experiment in transmission of the disease from goat to man

nated frequently not only by sera from patients with Malta fever but by many "normal" sera as well The present study concerns a strain of *M melitensis* with all the typical cultural characteristics which was agglutinated only feebly by convalescent Malta fever serum whereas five other strains were agglutinated in titers of 1 1 000 to 1 5 000 An immune serum however prepared from this strain failed entirely to agglutinate the other five strains whereas it agglutinated the homologous strain in a titer of 1 500 Thus they had separated an immunologically different strain of *M melitensis* which they designated "paramelitensis" by analogy to parameningococci and paradysentery bacilli This work was later extended ("Identification des paramelitenses par l'épreuve de la saturation des agglutinins" *ibid* p 1052) by agglutination and absorption tests

26 LARSON W P and SEDGWICK J P The complement fixation reaction of the blood of children and infants using the Bacillus abortus as antigen Am J Dis Child 6:326 1913

From the work of Cotton and Schroeder (Ref 23) the writers knew that 10 per cent of market milk contains *B abortus* and also that animals may be infected per os They wondered therefore whether humans were ever infected and they examined the blood of 425 children by complement fixation using *B abortus* as antigen Of these 425 they found 73 positive The antibodies could also be absorbed by suspensions of the bacilli These investigators definitely raised the question of human infection with *B abortus* but they went no further and made no suggestion of the occurrence of undulant fever in man as a result of infection with it

27 Report of the chief of the Bureau of Animal Industry Annual Reports of the Department of Agriculture for the Year Ended June 30 1914 p 86 Washington Government Printing Office 1914

The report includes reference to premature hairless pigs which were sent in to the Department of Agriculture for examination "Cultures made from liver stomach contents and kidneys revealed an organism resembling Bacillus abortus in cultural and morphological characteristics These cultures when used as antigens in both agglutination and complement fixation tests gave the same results with two known negative two known positive and with unknown bovine sera as were obtained with an antigen prepared from B abortus of Bang from bovine origin" This seems to be the first report of a porcine strain Whereas the finding is often attributed in the literature to J Traum (see for example H J Harris *Brucellosis* [2d ed New York Paul B Hoeber 1950] p 9) his name is not mentioned in the report which emanated from the Pathological Division under the direction of Dr John R Mohler Actually I S Good and W V Smith ("Bacillus abortus [Bang] as an etiological factor in infectious abortion of swine" J Bact 1 415 1916) seem to have first isolated from the afterbirth of an aborting sow and from numerous other tissues organisms which they were unable to distinguish from *B abortus*

C P Beattie and R M Rice ("Undulant fever due to Brucella of the porcine type—Brucella suis J A M A 102 1670 1934) report a milk borne epidemic of 30 cases of undulant fever due to *Brucella suis* The organism was obtained by blood culture from 6 to 14 patients and from the milk of one cow Infection with porcine strains seemed especially common in Iowa A V Hardy C F

in the milk of perfectly healthy cows The writers did not definitely link these milk borne bacilli to any human disease but they did think that the germ forms another link in the long chain of facts that point unmistakably to the proper pasteurization of all milk as a measure essentially necessary for the protection of public health " A few years later E C Fleischner and K F Meyer ("Observations on the presence of the Bacillus abortus bovinus in certified milk" Am J Dis Child **14** 157 1917) carefully reviewed the whole subject and added observations of their own from which they concluded "B abortus is for practical purposes always present in the certified milk produced in the San Francisco Bay regions "

24 SMITH Theobald and FABYAN Marshall Ueber die pathogene Wirkung des Bacillus abortus Bang Centralbl f Bakt **61** 549 1912

After the appearance of the report of the British Commission i was assumed that all Malta fever resulted from drinking goat s milk or other contact with goats Until the work of Smith and Fabyan infection with *B abortus* remained a strictly veterinary problem No relation was suspected between the two in the causation of disease With material from contagious abortion Smith and Fabyan were able to produce a chronic disease in guinea pigs featured by enlarged and engorged spleen enlarged lymph nodes and small nodules in the liver The disease was passed in series through guinea pigs and *B abortus* was isolated in pure culture from the lesions which were reproduced by it The disease ran as long as *eleven months without very drastic external appearances* Sometimes there were overt lesions of bones and joints Smith and Fabyan found microscopically "a chronic inflammatory process closely resembling tuberculosis" There were foci of epithelial cells and lymphoid cells occasionally with necrotic centers The details must be read in the original communication Bacilli were found especially in spleen but also in lymph nodes bone marrow liver kidney and lung and were grown from the lesions Smith and Fabyan concluded first that contagious abortion was caused in America as in Europe by *B abortus* Bang Second they suggested that the overt lesions of contagious abortion were not always primary but were secondary to slow general infection of the sort described in guinea pigs "That the Abortbacillus appears in milk is very probable" Conclusions (1) B abortus Bang is most probably the only cause of contagious abortion (2) B abortus produces in guinea pigs a peculiar generalized diease which rarely leads to death It resembles tuberculosis and is characterized by chronic interstitial new growths which *for the most part consist* of epithelial and lymphoid cells (3) B abortus can be present in milk and *it is* therefore indicated to investigate whether it has any causal relationship with any chronic disease of man "

M Fabyan ("A contribution to the pathogenesis of B abortus Bang II J M Res **26** 441 1912) a little later wrote up much the same material in English He described in great detail the pathology of the disease produced in guinea pigs

25 NEGRE L and RAYNAUD M Melitensis et paramelitensis Compt rend Soc de biol **72** 791 1912

The authors had already shown ("Sur l agglutination du Micrococcus melitensis par les serums humains " *ibid* **70** 472 1911) that *M melitensis* was aggluti

30 SMITH Theobald A characteristic localization of Bacillus abortus in the bovine fetal membranes J Exper Med 29:451 1919

The elucidation of the pathologic histology of Brucella infection was opened by the observations of T Smith who found *B abortus* in the epithelial covering of the chorion He noted that the more or less specific localization and multiplication of bacteria within cells not having phagocytic functions had been demonstrated in leprosy and syphilis E W Goodpasture and K Anderson ("The problem of infection as presented by bacterial invasion of the chorio allantoic membrane of chick embryos" Am J Path 13 149 1937) confirmed these findings in chick embryos inoculated with Brucella They noted that the bacilli enter ectodermal epithelial cells and proliferate there as they do in chorionic epithelium of the calf G F Buddingh and F C Womack ("Observations on the infection of chick embryos with Bacterium tularense Brucella and Pasteurella pestis" J Exper Med 74:213 1941) described the growth of Brucella in chick embryos more in detail confirming the findings of Goodpasture and Anderson They also described involvement of the endothelial cells lining the blood vessels K F Meyer ("Observations on the pathogenesis of undulant fever essays in biology [Berkeley and Los Angeles University of California Press 1943] p 439) described the pathologic histology in a laboratory worker who died within eleven days of an acute septicemia with *Brucella suis* "First and foremost is the intracytoplasmic multiplication of the bacteria in the epithelium of Bowman s capsule and the convoluted tubules This selective intracellular parasitism in mesenchyme cells of various organs is doubtless of greatest significance in the pathogenesis of Brucella infections There is no proof that the brucellas multiply in the blood stream Their presence in macrophages and polymorphonuclear leukocytes is justly attributed to phagocytosis Once in the cytoplasma they find conditions favorable for multiplication and protection against phagocytosis" Meyer gives an interesting and detailed analysis of the problems of pathogenesis of Brucella infection

Further studies along this line are those reported by W W Spink ("Pathogenesis of human brucellosis with respect to prevention and treatment Ann Int Med 29 238 1948) R D Sundberg and W W Spink ("Histopathology of lesions in bone marrow of patients having active brucellosis" Blood Suppl 1 p 7 1947) W W Spink F W Hoffbauer W W Walker and R A Green (Histopathology of the liver in human brucellosis" J Lab & Clin Med 34 40 1949) and M Ruiz Castenada ("Studies on the pathogenesis of brucellosis" Proc Soc Exper Biol & Med 64 298 1947)

31 KEEFER Chester S Report of a case of Malta fever originating in Baltimore Maryland Bull Johns Hopkins Hosp 35 6 1924

Z Khaled ("A comparative study of bovine abortion and undulant fever from the bacteriological point of view" J Hyg 20 319 1921) raised the question of "whether or not B abortus being so closely related to B melitensis is capable of producing an undulant or other form of fever in man" Without definite proof he reported having seen cases in Egypt "which have never had a chance of ingesting goat s milk and yet suffered from typical melitensis fever confirmed by laboratory diagnosis" Still earlier C Kennedy ("Preliminary notes on the presence of agglutinins for the Micrococcus melitensis in the milk and blood

Jordan and I H Borts (Undulant fever further epidemiological and clinical observations in Iowa J A M A 107 559 1936) found that 70 per cent of 124 cases were caused by this type C F Jordan and I Borts (Brucellosis and in fection caused by three species of Brucella Am J Med 2 156 1947) more recently reviewed the subject

28 FLEISCHNER E C and MEYER K F The bearing of cutaneous hy persensitiveness on the pathogenicity of the Bacillus abortus bovinus Am J Dis Child 16 268 1918

The authors noted the resemblance between the experimental lesions of *B abor tus* in guinea pigs and those of tuberculosis (Ref 24) Hence they did skin tests with extracts of *B abortus* and with abortus bacilli Guinea pigs with lesions in variably gave a positive skin reaction Guinea pigs which had been injected with dead cultures or in which no disease developed always gave a negative skin test The author therefore drew analogies to tuberculin testing and concluded that a positive skin test to abortin indicated active infection On the other hand In a series of seventy five infants fed on a high bacillus abortus containing milk cutaneous hypersensitiveness was not present and the writers regarded this as suggestive evidence that *B abortus bovinus* was not highly pathogenic for infants

29 EVANS Alice C Further studies on Bacterium abortus and related bacteria II A comparison of Bacterium abortus with Bacterium bronchi septicus and with the organism which causes Malta fever J Infect Dis 22 580 1918

Since it had been shown that the Malta fever organism commonly infected goat s milk on the island of Malta and that *B abortus* commonly infected cow s milk in this country it occurred to Evans to make a detailed comparison of the two Using elaborate cultural and immunologic tests she found that the organism which causes Malta fever is unquestionably a rod form and should be called Bact melitensis But melitensis is very closely related to Bact abortus The only test which has been found to distinguish these two organisms is the agglutination of Bact melitensis in higher dilutions of melitensis serum than will agglutinate Bact abortus The agglutination tests as they have been used to diagnose infections of Bact melitensis in goats and human subjects cannot be relied on to distinguish one from the other" This was pioneer work in pointing out the similarity of the bacteria which cause Malta fever and con tagious abortion of cattle Evans continued and elaborated her studies ("The serological classification of Brucella melitensis from human bovine caprine porcine and equine sources" Pub Health Rep 38 1948 1923)

M L Fusier and K F Meyer confirmed and elaborated Evans work (Prin ciples in serological grouping of B abortus and B melitensis correlation be tween absorption and agglutination tests" J Infect Dis 27 185 1920) and suggested that the "B abortus and B melitensis group be given generic rank in the Bacteriaceae family as the genus Brucella Meyer also pursued these studies with E B Shaw (A comparison of the morphological cultural and biochemical characteristics of Br abortus and Br melitensis studies on the genus Brucella" J Infect Dis 27 173 1920)

33 KRISTENSEN Martin and HOLM Per Bakteriologische und statistische Untersuchungen uber Febris undulans in Danemark Centralbl f Bakt 112:281 1929

The authors give a critical discussion of the relation of infection with *B abortus* to abortion in women They are skeptical about such an infection playing a significant part in human pathology although they allude to the case of a woman who aborted in the seventh month from whose placenta the abortus bacillus was grown although none was recovered from the organs of the fetus C. M Carpenter and R Boak (Isolation of Brucella abortus from a human fetus" J.A.M.A 96:1212 1931) later isolated *B abortus* from the placenta and the fetal organs of an early abortion in a woman who did not have undulant fever They given an exhaustive review of the literature on the finding of abortus in the generative organs of humans and of various animals but leave undecided the case for *B abortus* playing an important role in human abortion [5]

34 SHARP William B Pathology of undulant fever Arch Path 18 72 1934

The morbid anatomy of brucellosis is comprehensively reviewed with bibliography The writer points out the scant material in the literature and the paucity of distinctive gross lesions "The most essential item in the general pathologic alteration is a proliferation of cells belonging to the reticulo-endothelial system" H J Harris in his book *Brucellosis* (*loc cit*) gives a long list of all the lesions which have been described in various organs (p 91) and then a detailed discussion with references to the literature

35 CARPENTER Charles M and BOAK Ruth A The treatment of human brucellosis a review of current therapeutic methods Medicine 15 103 1936

The writers give a comprehensive review with literature of the methods of treating brucellosis before the antibiotic era They point out the difficulty of evaluating any therapeutic measure in a disease which runs such a variable course both as to time and as to severity They discuss vaccine therapy serum therapy therapy with toxic filtrates therapy with various chemicals such as dyes arsphenamines etc foreign protein therapy and therapy with induced fever The conclusion from all of this is "A successful method for the treatment of brucellosis still awaits development for as yet no therapeutic agent has been found which has been proved to alter to a significant degree the natural course of the disease"

36 CALDER R M STEEN C and BAKER L Blood studies in brucellosis J.A.M.A 112:1893 1939

Careful studies of the blood counts were made in several hundred cases The leukocytes were normal diminished or increased Active lymphocytosis was the most striking feature encountered

[5] Dr Charles E McLennan professor of obstetrics and gynecology at Stanford University tells me that as of today (1956) local infection with *B abortus* is not considered significant in human abortion.

serum of cows in London" J Roy Army M Corps 22 9 1914) referred to two cases of undulant fever in people who had never been out of England It remained for Keefer however to report the first case of a disease in man corresponding to Malta fever due to an organism belonging to the abortus group [4] Keefer's patient a laboratory worker is of great interest He ran a typical undulating fever and between October 19 and January 10 yielded thirteen positive blood cultures with one to six colonies per cubic centimeter of Brucella The infection was probably due to cow's milk and by appropriate serologic tests Keefer showed that the organism was of the abortus type Thus the melitensis and abortus types were finally brought together clinically as well as immunologically Alice Evans was also hot on the trail (Malta fever cattle suggested as a possible source of infection following a serological study of humans" Pub Health Rep 39 501 1924) as a result of comparative study of human sera but she described no actual patients

Other cases of "Malta fever" due to *B abortus* were soon reported such as those of C M Carpenter and H E Merriam (Undulant fever from Brucella abortus" J A M A 87 1269 1926) who described two typical instances in which the organism was isolated from the blood and proved by agglutination absorption tests to be the abortus variety "Contagious abortion and undulant fever were also discussed at a meeting of the Royal Society (Brit M J 1 554 1925)

32 HARDY A V HUDSON Margaret G and JORDAN C F The skin as a portal of entry in Br melitensis infections J Infect Dis 45:271 1929

The frequency of undulant fever in the employees of a meat packing plant suggested to the writers that Brucella infection through the skin might be a common occurrence Guinea pigs were readily infected by spreading culture on the shaved or clipped skin That such infection was not due to organisms which entered via the digestive tract is made clear by the much lower occurrence of infections when culture material was actually fed by mouth The significance of the skin route seemed to be confirmed by the frequency of infection in workers in the packing house where those who actually killed and cut the animals had the disease much more frequently than those who worked in the offices or elevators or handled boxes carried meat etc

The importance of infection through the skin had been recognized long before the present work by the British Commission (Ref 21)

[4] In regard to Keefer's case Huddleson (op cit p 68) says "Duncan [J T Duncan in discussion of "Contagious abortion and undulant fever Brit M J 1 544 1925] was the first to recognize and report cases of Brucellosis due to Br abortus Duncan reports a case in a brief paragraph in which he states conservatively that the weight of the evidence pointed to B abortus as the cause of Rhodesian undulant fever in man but "experimental proof was still awaited as also was a really trustworthy test to distinguish B abortus from B melitensis" As to Keefer's culture Huddleson states "Several years later the author had an opportunity to study this culture and it was then found to be Br suis" At any rate Keefer reported the first case of what was clinically Malta fever in which a member of the Brucella group other than melitensis was proved to be the cause

either drug used separately failed "A prolonged constant septicemia promptly ceased," and no relapse occurred in a seventeen month period W W Spink W H Hall J M Shaffer and A I Braude ("Human brucellosis its specific treatment with a combination of streptomycin and sulfadiazine" J.A.M.A 136 382 1948) following successful trials in chick embryos (Ref 37) treated nine patients with a combination of sulfadiazine and streptomycin with "more satisfactory results than any other therapy used to date" They advised streptomycin intramuscularly in doses of 0 5 gm every 6 hours for 7 days and sulfadiazine with an initial oral dose of 4 gm and then 1 gm every 4 hours for at least 2 weeks These writers later amplified their results ("Treatment of brucellosis with streptomycin and a sulfonamide drug" *ibid* 139:352 1949) Although not absolutely secure this form of therapy is followed by fewer relapses and the appearance of streptomycin resistant Brucella has not occurred

40 SPINK W W BRAUDE A I CASTENADA M R and GOYTRA R S Aureomycin therapy in human brucellosis due to Brucella melitensis J.A.M.A 138:1145 1948

Working in Mexico with patients ill with undulant fever due to *B melitensis* in contrast to those seen in Iowa with disease due to *B abortus* the writers found aureomycin by mouth the most effective remedy However they have certain reservations and in an addendum at the end of the paper there is some tempering of enthusiasm because of relapses Enthusiastic reports also soon appeared from various sources such as those of M S Boyer E B Schoenbach R M Wood, and P H Long ("The treatment of acute brucellosis with aureomycin" Bull Johns Hopkins Hosp 84:444 1949) and of V Knight F Ruiz Sanchez A Ruiz Sanchez and W McDermott ("Aureomycin in typhus and brucellosis" Am J Med 6 407 1949) Later W W Spink, W H Hall and R Magoffin ("Follow up study of therapy in forty-eight culturally proved cases of brucellosis streptomycin and sulfadiazine aureomycin and chloramphenicol [chloromycetin[R]]" Arch Int Med 88 419 1951) reported follow up studies of 48 patients treated with various combinations of antibiotics and sulfonamides The results with streptomycin and sulfadiazine and with aureomycin seemed about equal about one half recovering promptly and remaining well with chloramphenicol the results were not quite so good So too in an elaborate study E M Yow and W W Spink ("Experimental studies on the action of streptomycin aureomycin and chloromycetin on Brucella" J Clin Investigation 28 871 1949) found strains of *B abortus B suis* and *B melitensis* all sensitive in vitro to the three antibiotics The action of streptomycin was bactericidal while aureomycin and chloromycetin were bacteriostatic. A little later W E Herrell and T E Barber ("A new method for treatment of brucellosis" J A M A 144 519 1950) reported good results from treatment with a combination of aureomycin by mouth and streptomycin intramuscularly

41 KNIGHT V SANCHEZ F R and SANCHEZ A R Terramycin in the treatment of human brucellosis Arch Int Med 87 835 1951

In the hope of finding an antibiotic therapy for brucellosis which would not be followed by relapses the authors used terramycin which proved highly effective in the treatment of the acute manifestations There were however a significant number of relapses

37 JONES D METZGER H J SCHATZ A and WAKSMAN S A Control of Gram negative bacteria in experimental animals by streptomycin Science **100** 103 1944

It was inevitable that streptomycin an antibiotic potent against Gram negative bacteria would be tried against Brucella Waksman the discoverer of this antibiotic himself here reports the protection of 15-day chick embryos against infection with Brucella by treatment with streptomycin when untreated controls succumbed A little later I Live F G Sperling and E L Stubbs (Effect of streptomycin on experimental brucellosis in guinea pigs Am J M Sc **211** 267 1946) found that 2 000 units of streptomycin daily in six doses seemed to eliminate the infection from most guinea pigs when treatment was begun 1 week after infection

W H Hall and W W Spink ("Therapy of experimental Brucella infection in the developing chick embryo I Infection and therapy via the allantoic sac" J Immunol **59** 379 1948) later developed a method for testing therapeutic agents against Brucella by injecting them into the allantoic sac of the developing chick embryo Sulfadiazine and streptomycin in combination were found to be more effective against *B abortus* and *B suis* than either drug alone J M Shaffer and W W Spink (III The synergistic action of streptomycin and sulfadiazine" J Immunol **60** 405 1948) with the same technique soon showed that such combined action represented a true synergism R Magoffin D Anderson and W W Spink (IV Therapy with aureomycin" J Immunol **62** 125 1949) explored aureomycin alone and in combination with other agents

38 REIMANN H O PRICE A H and ELIAS W F Streptomycin for certain systemic infections and its effect on the urinary and fecal flora Arch Inst Med **76** 269 1945

In contrast to its apparent effect in experimental brucellosis (Ref 37) streptomycin has been reported of doubtful value in human infection Thus Reimann states that treatment with streptomycin was inconclusive in three cases D E Nichols and W E Herrell (Streptomycin its clinical use and limitations" J A M A **132** 200 1946) also found the results of treatment of brucellosis disappointing in a number of cases although in some it had a temporary suppressive effect However W H Hall and W W Spink (In vitro sensitivity of Brucella to streptomycin development of resistance during streptomycin treatment" Proc Soc Exper Biol & Med **64** 403 1947) found most strains of Brucella sensitive to streptomycin in the test tube although one strain from a patient with Brucella endocarditis became resistant during therapy and G H Finch ("Streptomycin therapy in undulant fever" Am J Med **2** 485 1947) thought that he had obtained favorable results in several cases

39 *PULASKI E J and AMSPACHER W H Streptomycin therapy for* certain infections of intestinal origin New England J Med **237** 419 1947

The authors treated two acute cases of brucellosis with a combination of streptomycin and sulfonamide therapy which seemed to produce a cure C W Eisele and N B McCullough independently tried the same device the simultaneous use of streptomycin and sulfadiazine they thought was curative when

PNEUMOCOCCAL PNEUMONIA

Bacteremia	Ref 49
Bacteriology	Refs 8 9 13 14 15 21 23 24 48
Chlorides suppression	Ref 5
Circulation	Refs 42 43
Clinical description	Refs 1 2, 4 5 7 38 61
Complications	Refs 10 22 38
Diagnosis physical	Refs 1 4 7
Epidemiology	Refs 17 19 39
Etiology bacterial	Refs 8 9 13 15 16 18 21 23 24 48
General	Refs 7 38 59 61
Immunity	Refs 23 25 26 28 32 34 39 47 50 51 54 57 63
Pathology	Refs 1 2 3 5 6 55 57
Penicillin therapy	Ref 62

(*Continued on following page*)

42 ABERNETHY, Robert, and SPINK Wesley W The influence of cortisone and adrenocorticotrophic hormone on brucellosis I Cortisone in experimentally infected animals J Clin Investigation 31 915 1952

In mice with acute brucellosis steroids converted a relatively mild infection into a fulminating and fatal illness In contrast, cortisone did not appear to alter the course of the disease or the tissue reactions in chronically infected animals In contrast also ACTH administered to a patient with acute brucellosis (W W Spink and W H Hall II Adrenocorticotrophic hormone [ACTH] in acute and chronic human brucellosis" J Clin Investigation 31 958 1952) was accompanied by prompt and remarkable improvement although the blood cultures remained positive "The only indication for cortisone or ACTH at the present time in acute or chronic brucellosis is in patients who are quite ill and toxic And even then treatment should be carried out only for a few days and simultaneously with antibiotic therapy"

43 SPINK W W Some biological and clinical problems related to intracellular parasitism in brucellosis New England J Med 247 603 1952

In an important paper Spink puts his finger on the difficulty involved in all chemotherapy and antibiotic therapy of brucellosis namely the intracellular situation of the parasite which guards it against the action of chemicals antibiotics and sera which may be lethal in the test tube He reviews and analyzes the whole subject with comprehensive bibliography In another paper (J M Shaffer C J Kucera and W W Spink "The protection of intracellular Brucella against therapeutic agents and the bactericidal action of serum" J Exper Med 97 77 1953) Spink and his associates devised a method for the study of intracellular Brucella in vitro Such Brucella were protected to a great extent against the action of antibiotics Actually no method of therapy so far devised has completely overcome this barrier It is apparently bacteria protected against attack within cells which cause the frequent relapses in spite of therapy

44 SPINK W W McCULLOUGH N B HUTCHINGS L M and MINGLE C K Diagnostic criteria for human brucellosis J A M A 149 805 1952

This paper is a critical appraisal by experts of the various diagnostic tests which have been used They point out that the only unimpeachable proof of brucellosis is isolation of the organism Agglutination in a titer of 1 320 or over allows a presumptive diagnosis The skin test gives insecure results

PNEUMOCOCCAL PNEUMONIA

MODERN knowledge of lobar pneumonia begins clearly and precisely with Laennec Before Laennec all was vague and indeed almost medieval At one stroke the discoverer of auscultation the leader of the great French school of clinician pathologists brought order out of confusion and gave a description of the disease which is still reflected in the textbooks of today However Laennec and his followers thought of pneumonia as they did of *a* pleurisy or *a* fever or *a* diarrhea as a general entity it was not until the second half of the nineteenth century that the concept of "croupous" or "lobar pneumonia" as a specific disease emerged and this concept was confirmed and established in the last quarter of the century by the discovery of the pneumococcus The early literature is immense and no purpose is served by giving more than several illustrative references

The invaluable volumes of White (Ref 59) and of Heffron (Ref 61) contain extensive bibliographies for which every student of pneumonia must feel grateful. Our own references try to cover the high spots of the development of knowledge through the early days of bacteriology the era of serum therapy and finally of the conquest of the disease by modern antibiotics In making a selection from the vast literature on the biology of pneumococcus—types somatic protein and capsular carbohydrate behavior in the body—we have tried to pick out only those studies which have a fundamental bearing on clinical problems

1 LAENNEC R T H Traité de lauscultation médiate et des maladies des poumons et du cœur 1 393 2d ed Paris J S Chaude 1826

As in all his other descriptions Laennec is the supreme master In simple vivid language he gives a picture of pneumonia to which little can be added today He enumerates three stages—engorgement hepatization and purulent infiltration (resolution)—with the auscultatory signs and with a brilliant discussion of the symptoms and course of the disease It is obvious that Laennec s account still influences modern textbooks The character of the breathing says Laennec depends on the functional disturbance in the lung the sputa are described in detail Although the term "purulent infiltration was an unfortunate one and probably meant no more than normal resolution actual abscess formation seems to have been common in Laennec s day Long exposure to cold is emphasized as a cause of the disease The Russian who leaves his stove to roll in the snow the bakers who practically naked emerge from the torrid atmosphere of their ovens to expose themselves to a cold several degrees below zero are not usually taken with pneumonia but the *porte faix* who stand for a long time at street corners are often attacked Laennec recognized epidemics of pneumonia of unknown cause

Treatment as in all contemporary accounts was irrational the diet of only sugar and mucilaginous substances bleeding tartar emetic etc are discussed at length

The original account should be read by every student

given for various procedures such as the use of ammonia to prevent heart clots has little meaning today

7 JÜRGENSEN Theodor Kruppose Pneumonie *In* Handbuch der speziellen Pathologie und Therapie ed H v ZIEMSSEN 5:3 Leipzig 1874

This article of 183 pages is a classic and deals with every phase of lobar pneumonia Modern in tone no better discussion of the subject appeared in the next thirty five years Jurgensen clearly defines lobar pneumonia as a specific disease In contrast to the usual opinion of the time he is convinced that it is an infection "Croupous pneumonia is a general illness not a local one The inflammation of the lung is only a main symptom the general phenomena are not to be explained by the local lesion The assumption of a specific etiologic agent is necessary Croupous pneumonia belongs then to the group of infectious diseases Not all inflammation producing agents can cause croupous pneumonia It takes a something with specific characteristics—just as with typhoid"

There are comprehensive discussions of "etiology" (cold was just a predisposing factor not the "frigus unica pneumoniae causa") of epidemiology and of vital statistics The pathological description is complete the clinical account lucid and objective Legends such as that of "critical" days are disposed of Treatment is essentially expectant Jurgensen erred in believing that death was due to a specific cardiac weakness and he directed his therapy toward stimulating" the heart He thought bleeding and antiphlogistics accomplished this Interestingly enough the doctrine that patients with lobar pneumonia died of circulatory failure dominated therapeutic thinking until dispelled many years later by Newburgh and his associates (Refs 42 43)

8 KLEBS E Beitrage zur Kenntnis der pathogenen Schistomyzeten VII Die Monadien Arch f exper Path u Pharmakol 4 409 1875

Klebs reviews the evidence in favor of lobar pneumonia as an infection Most important, he thinks is the appearance in outbreaks or epidemics and that in such outbreaks cases occur without the usual alleged precipitating causes such as exhaustion or exposure to cold In a number of instances he attempted at autopsy to secure uncontaminated material He found in lung and meninges little spheres about 0 8 μ in diameter which he was sure were organisms and not fat droplets He was able to grow these in "egg white" It is not clear just what these "monads" were but they showed a lively motility which would seem to prove that they were not pneumococci Although much quoted in the literature as the first isolation of pneumococcus the paper is unconvincing

9 EBERTH C J Zur Kenntnis der mykotischen Prozesse Deutches Arch f klin Med 28 1 1880–81

Eberth in the early years of the bacteriological era had made general studies of all sorts of infections In this article he describes (with autopsy) a typical case of lobar pneumonia in which a purulent meningitis was present In both lung and meninges cocci were demonstrated often in pairs or chains different from the "cocci of pyemia These organisms were almost surely pneumococci although Eberth did not go so far as to claim a specific etiological agent Koch also in a general discussion of clinical bacteriology (Robert Koch "Zur Untersuchung

2 STOKES William A Treatise on the diagnosis and treatment of diseases of the chest Part I Diseases of the lung and windpipe Dublin Hodges & Smith 1837

Stokes probably represented the best British clinical practice of the day His account of pneumonia is however, "transitional between the older vague descriptions and the new picture which was emerging as a result of Laennec s work Stokes leans heavily on Laennec and constantly refers to him He enumerates the usual stages of the disease—engorgement solidification and resolution—with related auscultatory signs much stress is placed on postpneumonic abscess and there is a separate section on typhoid pneumonia Under treatment bleeding following Louis is emphasized along with antimony in the form of tartar emetic Mercury is also mentioned It is obvious that knowledge was still in a rather primitive stage

3 ROKITANSKY Carl Handbuch der speziellen pathologischen Anatomie 2 84 Vienna Braumuller & Seidel 1842

The term "croupous pneumonia" was already in use Rokitansky following Laennec (Ref 1), recognized three stages engorgement hepatization and purulent infiltration The last seems to be simply normal resolution The pathological changes are vividly described and easily recognized

4 SKODA Joseph L Abhandlung uber Perkussion und Auskultation p 243 3d ed Vienna Braumuller & Seidel 1844

Skoda added to Laennec s auscultatory findings those of percussion One notes the intense interest in physical diagnosis at this time so that a pneumonia was thought of more as an anatomical process than as a specific disease

5 REDTENBACHER Wilhelm Beobachtungen am Harne bei Lungenentzundungen Ztschr d k k Gesellsch d Artze Wien 1 373 1850

Although Redtenbacher seems to have been the first to point out clearly the diminished excretion of chloride in pneumonia—a phenomenon universally recognized since then—a great deal of modern study has not fully elucidated the exact mechanism of this phenomenon (see Francis W Peabody Studies of inorganic metabolism in pneumonia with especial reference to calcium and magnesium J Exper Med 17 71 1913 F William Sunderman "Studies of serum electrolytes IV The chloride and nitrogen balances and weight changes in pneumonia J Clin Investigation 7 313 1929 T S Wilder and T G H Drake "Metabolism of chloride and total fixed base in pneumonia and the relation to salt and water retention J Clin Investigation 7 353 1929)

6 FLINT Austin A treatise on the principles and practice of medicine chap iv p 152 Philadelphia Henry C Lea 1866

Flint represented the best medical practice of his time in America and one is not surprised to find an excellent chapter on lobar pneumonia The pathology is well described in relation to history and physical signs There is no suggestion that Flint suspected the disease to be communicable He mentioned death from pulmonary embolus but regarded the clots as having been formed in the right ventricle and pulmonary artery Treatment was "symptomatic but the rationale

as Pasteur had obtained their material from a disease source whereas his was derived from the saliva of healthy people he saw no reason however why the disease should not be the same He speculated further on the presence in the mouth of pathogenic bacteria along with many harmless ones From a modern standpoint the type and the virulence of pneumococci in different salivas would account for Sternberg s variable findings

He also noted that the "virulence" of saliva was destroyed by boiling that it was lost when kept for 24 hours at 37 C or when carbolic acid was added or when the serum from a dead rabbit was filtered

13 FRIEDLANDER C. Ueber die Schizomyzeten bei der acuten fibrosen Pneumonie Virchows Arch path Anat 28:319 1882.

Friedlander s report the first of any real significance from the bacteriological standpoint concerns eight cases of lobar pneumonia The material was obtained at post mortem and consisted of stained sections The same sort of microorganisms were found in all—lance-shaped diplococci—often in tremendous numbers especially in red hepatization They were undoubtedly pneumococci Friedlander clearly showed that the cocci were found in large numbers in the lymphatics of the edematous interstitial connective tissue which ran from the margin of the hepatized tissue toward the air-containing parenchyma thus anticipating the modern work of Robertson (Ref 57) and others This finding was regarded as very important "It brings unequivocal proof that the micrococci get into the tissue juices and actually grow in living tissue" Are these micrococci the cause of pneumonia? asked Friedlander He felt that anatomical studies did not absolutely settle the question but thought that the fact that most pneumonias resulted from "cold" was not incompatible with a bacterial etiology cold might predispose to invasion by "pneumococci." This was the standard concept for many years until pneumococci were separated into groups (Ref 40)

14 [LEYDEN] Ueber infektiose Pneumonie Verhandl d Ver inn Med zu Berlin November 20 1882 *in* Deutsche med Wchnschr 9:52, 1883

The previous work had all been on post mortem material Leyden reported the finding of cocci corresponding to those described by Friedlander (Ref 13) in lung puncture fluid from a patient This was confirmed at autopsy At the same meeting Gunther reported finding diplococci by lung puncture in a patient very ill with pneumonia Gunther s drawing was said to show a capsule These observations were taken as evidence of the infectious nature of lobar pneumonia Maximilian Mátray ("Ueber Pneumoniecoccen" Wien med Presse 24 732, 766 1883) made systematic studies of the sputa of patients with lobar pneumonia and found typical lance-shaped diplococci in smears often in huge numbers He regarded these probably correctly as identical with the pneumonia coccus described by Friedlander another example of how confused the situation was at the time

15 FRIEDLANDER C Die Mikrococcen der Pneumonie Fortschr d Med 1 715 1883

Friedlander quickly extended the work discussed in his first paper (Ref 13) The characteristic cocci were found in some fifty cases Friedlander reported

von pathogenen Organismen" Mitt a d K Gsndhtsamte 1 46 1881) described and pictured cocci the nature of which is uncertain in a pneumonic lung

10 OSLER, William Infectious (so-called ulcerative) endocarditis Arch Med 5 44 1881

"Under the terms *diphtheritic ulcerative malignant septic* or *infectious* endocarditis *arterial pyaemia mycosis endocardii* physicians now recognize one of the most formidable of cardiac affections characterized by a peculiar morbid process on the valves blood contaminations constitutional symptoms of the typhoid or pyaemic types and usually associated with multiple emboli" In this classical article Osler clearly notes the association of endocarditis and meningitis with lobar pneumonia and describes masses of "micrococci" on the valves Osler *in contrast to many contemporary bacteriologists was himself uncertain* as to the significance of these cocci

11 *PASTEUR L* avec la collaboration de *MM CHAMBERLAND* et ROUX. Sur une maladie nouvelle provoquée par la salive d un enfant mort de la rage Compt rend Acad de sc 92 159 1881

Pasteur inoculated a "little mucus" from the mouth of a child dead of rabies into rabbits which died within a day or two Saliva and blood from these rabbits was injected into others which also died promptly Pasteur passed the disease on through a number of generations He soon noticed that "the blood of the animals was invaded by a microscopic organism of very curious properties" *There follows a beautiful description of lance-shaped diplococci* "Each of these little bodies is surrounded by a sort of aureole produced by a mucoid substance resembling the cocoon of the silkworm" Pasteur did not believe *this disease or organism had anything to do with rabies "a different disease of* long incubation period" He left the problem with the thought that further work was essential

At the meeting of the Academy of Medicine of March 29 *1881 the secretary* read a report for M Vulpian (Bull Acad méd Paris 2d ser 10 394 1881) in which he described the death of rabbits a day or two after subcutaneous injection of saliva from *healthy* men with passage of the disease by injection of blood from the infected rabbits and the finding of organisms corresponding to Pasteur s in the blood He thus furnished a link between the work of Pasteur and that of Sternberg *(Ref 12)*

12 STERNBERG George M A fatal form of septicemia in the rabbit produced by the subcutaneous injection of human saliva Nat Board Health Ann Rep 1881 p 87

Sternberg, *following Pasteur found that 1 or 2 cc of his own sputum injected* subcutaneously into rabbits "infallibly produces death within 48 hours" Variable results were obtained with the saliva of others However the saliva of "Dr S" *always showed exceptional virulence The "course of the disease and* the post mortem appearance indicate that it is a form of septicemia" The blood and other tissues contained a vast number of micrococci similar to the organism described by Pasteur Sternberg *was puzzled because other experimenters such*

the rabbit " There can be no doubt that Talamon deserves credit for early accurate work on the subject and one is not surprised that the French often speak of Frankel s observations as a confirmation of those of Talamon The paper was read at the November 30 meeting of the Société Anatomique of Paris

17 EMMERICH Rudolph Pneumoniecoccen in der Zwischendeckenfullung als Ursache einer Pneumonie-Epidemie Fortsch d Med., 2:153 1884

Pneumonia had been epidemic at the Amberg prison for several months From dust in the floor crevices Emmerich was able to cultivate "pneumonia cocci" and to kill rabbits with culture material No pneumonia cocci were recovered from dust of rooms where there had been no cases of pneumonia A number of other contemporary workers published similar findings (for summary see Washbourn s Croonian lectures [Ref 32]) some of which are not very convincing although confirmed later by the comprehensive work of Stillman (Ernest G Stillman "Further studies on the epidemiology of lobar pneumonia " J Exper Med 26 513 1917) Stillman found that from the dust of houses in which cases of Types I and II lobar pneumonia had been ill pneumococci of the same sort could be recovered In dust from rooms in which there had been no cases of pneumonia pneumococci were found in 29 per cent of sixty two specimens These were almost always of the types normally found in the mouth The epidemiological implications are discussed

18 FRÄNKEL, A Die genuine Pneumonie Verhandl d Kong f inn Med 3d Cong p 17 Wiesbaden J F Bergmann, 1884

Frankel speaking in a symposium on pneumonia on April 21 1884 succeeded in thoroughly confusing things First he reported in contradiction of Friedlander s experience (Ref 15) infection of *rabbits* by some but not all, strains of the "pneumonia coccus " He referred to Friedlander s observations on capsule formation and declared that there was another organism which also was encapsulated and closely resembled the pneumonia coccus to be found in the mouths of normal people This organism injected into rabbits often caused death in 24-48 hours and Frankel designated it the coccus of sputum septicemia (Refs 11 12) Frankel had no idea that this organism could be related to the cocci found in cases of lobar pneumonia and came to the conclusion that because similar organisms are found in normal saliva "it is not possible to characterize the pneumonia micrococcus as such "

Friedlander in discussion had no direct rebuttal but stuck to his guns Half a-dozen other prominent physicians talked but added nothing

19 MENDELSOHN Martin Die infektiose Natur der Pneumonie Ztschr f klin Med 7 178 1884

This comprehensive article begins with a review of the reported epidemics and outbreaks of pneumonia in various localities in military establishments in jails and in houses Convincing instances of spread by contagion are described The writer does not think that pneumonia is caused by bad weather since most cases occur in the spring He confirms previous bacteriological studies and agrees that there is a specific organism Mendelsohn contributes little in regard to the mode of transmission but notes that pneumonia recurs frequently in the same person

that one of his co workers Dr Gram of Copenhagen had succeeded in developing a method whereby the cocci were intensely blue stained in contrast to a faintly counterstained background He stated that Drs Gunther and Leyden were able to demonstrate the cocci in "pneumonia juice" obtained by lung puncture a procedure which was revived as a diagnostic measure many years later (Ref 48) Dr Gunther also noted that the cocci were surrounded by an unstained capsule (Ref 14) Friedlander studied the capsules extensively in material obtained by lung puncture at autopsy He concluded that the capsule was mucinous not an artifact but a product of the vital processes of the microorganism Capsules were less evident in material from late cases (after the fifth day) He presumed that encapsulated cocci would be found in the blood of severely ill patients Friedlander and his associates readily grew the organisms in pure culture on Koch s gelatin medium and subcultured them through many generations Gram positive diplococci were obtained in great quantity but in these culture strains no capsule was demonstrated However when the bacteria were injected into mice the animals all died within a day or so with innumer able *capsulated* organisms in blood lung and pleura Friedlander did not quite understand that he had produced a septicemia rather than simply a severe pneumonia with overflow into the blood stream and he was unable to infect rabbits He observed slight differences in size and shape and capsule formation in different animals under various circumstances Friedlander considered his findings strongly in favor of the "infectious" theory of lobar pneumonia

Anyone who studies this paper will be convinced that Friedlander saw and described the pneumococcus There were two puzzling features however Friedlander s coccus in distinction to true pneumococcus did not produce dis ease in rabbits and it grew profusely on almost any medium Also in some of his pictures rod shaped organisms are shown Frankel (Ref 23) promptly seized on these discrepancies to claim that Friedlander s organism was actually a bacillus and that it was quite different from the true pneumococcus which he Frankel had described so well Here is a mystery probably never to be solved Friedlander clearly began with pneumococcus All his many typical cases of lobar pneumonia could not possibly have been Friedlander pneumonia Some where along the line however things evidently became confused with another encapsulated organism—*Klebsiella pneumoniae* Frankel left no stone unturned to deprive Friedlander of any credit although Friedlander s name clearly de serves mention in the discovery of pneumococcus much more so than that of Weichselbaum (Ref 21)

16 TALAMON Ch Note sur le coccus lanceole de la pneumonie lobaire *fibrineuse Progr méd Paris* **11** *1030* *1883*

Talamon had been working on the pneumonia problem when Friedlander s paper (Ref 15) stimulated him to make a report He concluded with an admir able summary Lobar pneumonia is an infectious disease produced by the mul tiplication in the lung of a special microbe This microbe can be found in the pneumonic exudate from the living patient It is not in the blood except in cer tain cases probably very rare in the agonal stage It has a characteristic lanceo late form like a grain of wheat It can be isolated and grown in appropriate media One can produce with it experimentally fibrinous lobar pneumonia in

pneumococcus how then was it found so often by Friedlander in cases with all the earmarks of ordinary acute lobar pneumonia? (See Refs 13 15)

22 SENGER Emil Bakteriologische Untersuchungen uber die Pneumonie und pneumonische Metastasen Arch f exper Path u Pharmakol 20:389 1886

Senger felt that infection might spread from a primary pneumonia to other situations (metastases) He described especially meningitis endocarditis and pericarditis with the finding of typical cocci in all situations The concept of a bacteremia in association with many such metastases is not clearly brought out

23 FRANKEL, A Bakteriologische Mitteilungen Ztschr f klin Med 10 401 1886

The first part of this lengthy communication is essentially a confirmation and extension of the work of Pasteur and of Sternberg (Refs 11 12) There is a dis agreeable and quarrelsome tone and Friedlander especially seems to receive digs on every possible opportunity Frankel spoke of the organism obtained from saliva as the micrococcus of sputum septicemia Part 2 is concerned with the isolation of bacteria from lobar pneumonia Frankel was a careful and skilled bacteriologist and clearly isolated grew and defined the pneumococcus He in sisted that the organism isolated by Friedlander was something quite different partly because it did not kill rabbits and partly because of its profuse growth on gelatin He concluded that the micrococci f sputum septicemia were ubiq uitous and caused pneumonia if there was a precipitating cause especially cold and this doctrine of the genesis of pneumonia held sway until the dis covery of pneumococcus types (Refs 37 40)

As to Friedlander it seems clear that Frankel crowded him out of the picture and really forced on him the bacillus which for so long has borne his name Actually the weight of evidence as anyone who carefully studies Friedlander s papers will see (Refs 13 15) is that he clearly first saw and adequately de scribed the pneumococcus An authoritative and fair appraisal of the matter is to be found in White (Ref 59 pp 11 ff)

In this paper also Frankel makes perhaps the first observation on acquired pneumococcal immunity in rabbits An animal inoculated by scarification of the ear with culture material which survives has become immune and a second inoculation proceeds without reaction

24 FRANKEL A Weitere Beitrage zur Lehre von den Mikrococcen der genuinen fibrinosen Pneumonie Ztschr f klin Med 11 437 1886

Frankel describes a case of meningitis in association with lobar pneumonia he was able to recover the pneumococcus from the meninges The bacteriology of pneumococcus is further elaborated in this paper and Frankel notes the speed with which pathogenicity is lost in culture and that virulence can be restored by animal passage Frankel was an expert bacteriologist and undoubtedly deserves credit for clearly defining the characteristics of pneumococcus He also raises the question of whether every case of true lobar pneumonia is caused by one specific organism or whether the disease may be a reaction to a variety of germs He concludes that it is a specific disease always caused by pneumococcus

and that an attack apparently confers no lasting protection He speculates at length about the immunity of pneumonia with no final conclusion

This paper is especially valuable for its comprehensive review of contemporary ideas

20 STERNBERG George M The pneumonia coccus of Friedlander (Micro coccus pasteuri Sternberg) Am J M Sc 90 106 1885

This important paper illustrates well the confusion which existed as to the definition of the pneumococcus Sternberg wished to name the coccus of sputum septicemia (Refs 11 12) in honor of Pasteur he also considered the organism obtained from sputa of healthy people identical with the pneumonia coccus" of Friedlander He found that cocci obtained from lungs of lobar pneumonia patients corresponded to Friedlander s description He concluded The pneumonia coccus of Friedlander is identical specifically with the micrococcus previously described by me which is commonly found in normal human saliva" He thought that pneumonia was an autoinfection promoted by alcohol or "any other *depressing agency*

21 WEICHSELBAUM A Ueber die Aetiologie der akuten Lungen und Rippenfellentzundungen Med Jahrb N S 1 483 1886

In this article of nearly seventy five pages Weichselbaum gives a valuable review of the contemporary literature on the bacteriology and etiology of pneumonia which is followed by his own studies In typical lobar pneumonia the finding of *Diplococcus pneumoniae* was constant enough to make him feel with Frankel that it was the usual organism although in his conclusions Weichselbaum said The acute inflammations of the lung including genuine croupous pneumonia may be caused by a variety of bacteria Streptococci staphylococci and the organism of Friedlander which grew freely on all media at room temperature and was non pathogenic for rabbits were found in some cases No precise statement was made as to the type of disease although Weichselbaum isolated staphylococci from lobular rather than from lobar pneumonia Weichselbaum found pneumococci not only in the lungs but in the loose connective tissue of the neck in the paranasal sinuses and in the meninges there was evidently a bacteremia in these cases On the whole his work has been taken as a confirmation of Frankel An abbreviation of Weichselbaum s article appeared in the same year (Weichselbaum Ueber die Aetiologie und pathologische Anatomie der Lungenentzundungen Wien med Presse 27 820 1886) Later in still another long paper Weichselbaum ("Ueber seltenere Lokalization des pneumonischen Virus [Diplococcus pneumoniae] Wien klin Wchnschr 1 573 1888) reviewed the status of the pneumococcus and dwelt especially on lesions other than in the lung—meningitis endocarditis pericarditis arthritis etc He definitely formulated pneumococcal infection as a disease not necessarily confined to the lungs but rather a general infection with variable localization In reviewing Weichselbaum s work one sees no special reason why his name should have become attached to the pneumococcus Friedlander had a much better title

Friedlander s organism still remains a mystery It was pretty clearly not a true

28 WASHBOURN J W Experiments with the pneumococcus with special reference to immunity J Path & Bact 3:214 1896

Washbourn tried to bring some order into the subject He showed clearly that a fatal dose of pneumococci might be withstood if injected intraperitoneally in rabbits *along with* some serum from an "immune" animal He raised the question of different strains or races of pneumococci He showed that pneumococci grew well in immune serum but were clumped at the bottom of the tube instead of growing diffusely (Ref 31)

29 EYRE J W and WASHBOURN J W Resistant forms of pneumococcus J Path & Bact 4:394 1897

Bacterial dissociation is clearly described and the forms probably correspond to what were later designated as "rough" and "smooth" variants (Ref 53)

30 DENYS [J] Recherches sur le sérum antipneumococcique Ann Soc méd-chir d Anvers 2:51 1897

Denys in studying immunization of rabbits against pneumococci emphasized the role of *phagocytosis* "In summary immunity of the rabbit against the pneumococcus has its root in a modification of its serum It is true that the serum by itself is powerless but without it the leukocytes find themselves disarmed Immunization of rabbits was by this time well established and doses of 1 cc of serum could protect against 100 000 lethal doses of pneumococci Denys turned his attention to the preparation of serum in horses and goats and found that immune horse serum "1 Prevents infection 2 Cures infection when it is already under way 3 Neutralizes the toxins of the pneumococcus" The subject was beginning to assume an orderly aspect

31 BEZANÇON F and GRIFFON V Pouvoir agglutinatif du sérum dans les infections expérimentales et humaines à pneumocoques Compt rend Soc de biol 49 551 579 1897

Bezançon and Griffon made a special study of agglutination and found that immune serum diluted fifty fold might still be potent They also tried to develop a diagnostic test analogous to Widal s test for typhoid fever Pneumococci grown in serum from pneumonia patients in several instances grew in clumps with clear supernatant whereas there was a diffuse clouding of other sera Here then were the rudiments of the diagnostic test which later was so essential in typing pneumococci (Ref 40)

32 *EYRE J W H* and *WASHBOURN J W* Further experiments with Pane s antipneumococcus serum Brit M J 2 1247 1899

A number of workers had been preparing antipneumococcic serum in large animals and a few cases of human pneumonia had been treated (Refs 25 30) Eyre and Washbourn seem to have been the first to raise the question whether such sera might not be effective against all strains of pneumococcus They used a serum prepared by Pane of Naples and they found that it had considerable protective power for rabbits against only four out of five strains which were all similar in culture morphology and virulence They concluded There exist varieties of pneumococcus which at present can only be distinguished by the

Frankel loses no opportunity to be disagreeable to Friedlander whom he pursues quite unreasonably and sets himself up as the sole elucidator of the etiology of lobar pneumonia It was in this paper also that the name "pneumococcus first appeared [1]

25 KLEMPERER G and KLEMPERER F Versuche uber Immunisierung und Heilung bei der Pneumokokkeninfektion Berl klin Wchnschr 28 833 1891

The 1890s were the beginning of the golden age of serum therapy Doctors like stout Cortez when with eagle eyes he stared at the Pacific saw a vast ocean of opportunity and dreamed of curing all infections by appropriate sera The Klemperers were among the first to attempt systematically to immunize animals against pneumococcal infection As antigens they used culture filtrates treated in various ways and old pneumonic exudates apparently free of organisms There was no standard procedure and no fixed challenge dose An "immune" rabbit was said to resist 1 cc of the most virulent culture intravenously and its serum in turn was able to "cure pneumococcal septicemia" This serum also was capable of immunizing other rabbits against a challenge given as long as 4 weeks later There are lengthy speculations as to the mechanism of this immunity which have little meaning in the light of modern knowledge The Klemperers also made preliminary observations in man and found that a dose of pneumococci fatal for a rabbit could be injected subcutaneously into man with impunity G Klemperer later exposed his general ideas on immunization ("Die Beziehung verschiedener Bakteriengifte zur Immunisierung und Heilung" Ztschr f klin Med 20 165 1892)

26 KRUSE Walther and PANSINI Sergio Untersuchungen uber den Diplococcus pneumoniae und verwandte Streptococcen Ztschr f Hyg u Infektionskr 11 279 1892

This authoritative article of nearly one hundred pages summarizes to date views on the biology of pneumococcus and on pneumococcal infection and immunity It is of special importance since a phenomenon which is probably that of bacterial dissociation (Ref 53) is described for the first time Unfortunately most of the contemporary observations have little meaning in terms of modern immunology indeed many statements are hard to accept but they indicate the great surge of interest in preventing and curing infections by immunotherapy

27 MOSNY E Recherches experimentales sur la vaccination contre l infection pneumonique Arch med expér et anat path 4 195 1892

Mosny was unable in elaborate studies to confirm the work of the Klemperers and others at all points Animals could be protected against only relatively avirulent strains of pneumococcus from which spontaneous recovery might take place This shows how confused and unstandardized the subject was Mosny also showed that pneumococcus could grow in immune serum (see Ref 47)

[1] The chronology of the various names applied to the cocci of pneumonia is given in White (Ref 59 p 1) We have noted the principal contributions to the early bacteriological study of pneumonia Many more of lesser importance are reviewed by White (Ref 59 pp 6-11)

able to show that an immune horse serum which protected against many strains was totally ineffective with others The writers made a start at investigating this phenomenon systematically but it remained for Dochez and Gillespie so to extend pneumococcus typing that it became the basis for specific serum therapy (Ref 40)

38 CHATARD J A. An analytical study of acute lobar pneumonia in the Johns Hopkins Hospital from May 15 1889 to May 15 1905 Johns Hopkins Hosp Rep 15:55 1910

There was a great tradition in the Osler Clinic at Johns Hopkins of describing disease on the basis of careful firsthand observations Studies of malaria and of typhoid fever had already been made In this paper a very valuable clinical study of pneumonia is reported based on analysis of actual case records Subsequent papers by various authors in the same volume deal with the pathological anatomy of lobar pneumonia (p 81) the leukocytes in lobar pneumonia (p 89) terminal pneumonia (p 99) termination in recovery (p 103) pneumococcic endocarditis (p 139) pericarditis (p 155) empyema (p 167) thrombosis (p 189) arthritis (p 229) meningitis (p 247) and delayed resolution (p 277)

39 COLE Rufus Pneumococcus infection and immunity J A M A 69 693 1912

At the turn of the century the death rate from lobar pneumonia although it varied in different places and in different outbreaks was on the whole of the order of 25 per cent Furthermore the doctor was really helpless and could do little more than see to it that the patient had good nursing In the attempt to solve this colossal problem and develop effective methods of therapy the Rockefeller Hospital for many years took the lead in this country Rufus Cole director of the hospital from time to time wrote important and useful papers covering the progress of the work The present one was one of the first Other important summaries by Cole are Pneumococcus infection and immunity" Arch Int Med 14 56 1914 "Pneumococcus infection and immunity " New York M J 101 1 59 1915 "The nature of pneumonia " Proc Inst Med Chicago 9 2 1932 "The treatment of pneumonia " Ann Int Med 10 1 1936 Further papers by Cole are listed in Heffron s bibliography (Ref 61 pp 961–62) and detailed reviews of the literature may be found in Heffron (Ref 61 pp 204 ff) and in White (Ref 59 pp 427 ff)

40 DOCHEZ A R and GILLESPIE L J A biological classification of pneumococci by means of immunity reactions J A M A 61 727 1913

Although much work on this subject culminating in that of Neufeld and Handel (Refs 36 37) had been done abroad this paper remains the classical study Here it was clearly brought out by mouse protection and agglutination tests that as many as 65 per cent of pneumococci from patients with pneumonia fell into two distinct immunological types that 14 per cent more could be identified by cultural qualities as *Pneumococcus mucosus* (Type III) whereas only 22 per cent fell into a miscellaneous group The differentiation of these types served for years as a basis for developing specific therapeutic sera

Lister working at the same time in South Africa (F S Lister "Specific

action of antipneumococcus serum Work of this sort pointed inevitably to the necessity of systematically classifying pneumococcus types (Ref 40)

The whole subject of pneumococcus infection and immunity is well summarized to date in the Crooman lectures by J W Washbourn ("The natural history and pathology of pneumonia" Brit M J 2 1301 1378 1440 1528 1902)

33 NEUFELD F Ueber eine spezifische bakteriolytische Wirkung der Galle Ztschr f Hyg u Infektionskr 34 454 1900

Description of the lytic effect of bile on pneuococcus

34 NEUFELD F Ueber die Agglutination der Pneumococcen und uber die Theorien der Agglutination Ztschr f Hyg u Infektionskr 40 54 1902

In the course of this scholarly article on agglutination of pneumococci Neufeld describes the phenomenon of capsular swelling (quelling) when pneumococci are mixed with antiserum Since the phenomenon later turned out to be type specific it was adopted as a quick method of identifying pneumococci in sputum (F Beckler and P MacLeod "The Neufeld method of pneumococcus type determination as carried out in a public health laboratory a study of 760 typings" *J Clin Investigation 13 901 1934* G M Cooper and A W Walter "Application of Neufeld reaction to the identification of types of pneumococci" Am J Pub Health 38 491 1935)

35 ANDERS J M Serum therapy of pneumonia J A M A 43 1777 1904

In a useful paper Anders analyzes all the reported cases of pneumonia treated with the early sera which were of course not type specific He concludes that the reduction in mortality is so slight that general use of the sera is not warranted but that further efforts to devise an efficacious serum are strongly advisable

36 NEUFELD F and HANDEL Ueber Herstellung und Prufung von Antipneumococcenserum und uber die Aussichten einer spezifischen Behandlung der Pneumonie Ztschr f Immunitatsforsch u exper Therap 3 159 1909

The writers described methods of producing therapeutic immune serum from horses and of testing its efficacy They recognized the necessity of using large amounts of serum of isolating the organism from the patient and of seeing whether the available serum was protective against it

Neufeld and Handel summarized their views on the entire subject of serum therapy in pneumonia in a later paper ("Zur Frage der Serumtherapie der Pneumonie und der Wertbestimmung des Pneumococcenserums" Berl klin Wchnschr 49 680 1912)

37 NEUFELD F and HANDEL Weitere Untersuchungen uber Pneumococcen Heilsera Arb a d k Gsndhtsamte 34 293 1910

In the preceding decade a vast amount of work on antipneumococcal sera had been done This work is reviewed in White (Ref 59 pp 103 ff) Neufeld and Handel however devised a standard mouse protection test and with it were

as the pneumococci so constantly present in the mouths of healthy people infection should soon become universal A study was therefore made of the types of pneumococci in the salivas of healthy people and almost without exception members of the three virulent groups which usually cause pneumonia were absent while the pneumococci present were the relatively avirulent heterologous types Furthermore following acute lobar pneumonia the types causing the disease almost always disappeared shortly and were replaced by the usual mouth varieties Rarely was a carrier of fixed type pneumococcus encountered This important work at one stroke disposed of the long held idea that pneumonia was always an autogenous infection with strains of essentially harmless pneumococci carried in the mouth and that some "resistance lowering" factor allowed invasion to occur It became clear that infection usually resulted from a virulent strain which was not indigenous to the patient s upper air passages

45 DOCHEZ A R and AVERY O T The occurrence of carriers of disease-producing types of pneumococcus J Exper Med **22**:105 1915

After Dochez and Gillespie had isolated special types of pneumococci (Ref 40) from cases of pneumonia it was natural to inquire whether these disease producing organisms were the same as the pneumococci found in the mouths of so many healthy people The question was partly answered in the preceding reference (Ref 44) It now became necessary to find out more about the cir cumstances of the occasional carriage of virulent fixed types It turned out that for a time healthy persons intimately associated with cases of lobar pneu monia harbor the disease producing types of pneumococcus In every such instance the pneumococcus isolated has corresponded in type with that of the infected individual The existence of the carrier state [of virulent pneumo cocci] among healthy persons and among those recently recovered from pneu monia establishes a basis for understanding the mechanism by means of which lobar pneumonia spreads and maintains its high incidence from year to year Virgil P W Sydenstricker and Alan C Sutton ("An epidemiological study of lobar pneumonia " Bull Johns Hopkins Hosp **28** 312 1917) found in a group of workmen living in very close contact among whom there was a high inci dence of fixed type pneumonia that the presence of Types I and II pneumo cocci in the salivas of healthy men showed the remarkably high figure of 22 per cent Another extremely important study is that of E G Stillman "Further studies on the epidemiology of lobar pneumonia J Exper Med **26** 513 1917

An immense amount of work was subsequently done on the incidence of carriers of various types in relation to disease contact season climate etc This work is reviewed in detail with bibliography in Heffron (Ref 61 pp 342 ff) The summary by Maxwell Finland (Recent advances in the epi demiology of pneumococcal infections Medicine **21** 307 1942) is also useful

Even more recent interesting studies have been made such as those of W G Smillie Frank A Calderone and Jeane M Onslow "The epidemiology of the pneumococcus " Am J Hyg **37** 156 1943 They found in a group of 111 men who were followed through a season that pneumococci of many types were highly prevalent one man harbored seven different pneumococcus types in his

serological reactions with pneumococci from different sources Publ South African Inst M Res 1 1 1913) came to essentially the same grouping of pneumococcus strains

41 COLE Rufus The treatment of pneumonia by means of specific serums J A M A 61 663 1913

This is the earliest statement about serum therapy from the Rockefeller Hospital Hyperimmune sera prepared in horses were of such a potency that 1 cc protected animals against a million lethal doses *if injected with the bacteria* If serum was given *after* the infection was well under way even a huge amount was ineffective On these facts Cole enunciated two principles in the serotherapy of pneumonia First treatment should be begun as early in the disease as possible second large doses of potent serum should be used In practice 100 cc of serum were usually given intravenously once or twice daily Bloomfield later showed that blood stream invasion was the critical point and that as long as the blood culture was negative the effects of serum were good whereas if the blood culture was positive the results were poor regardless of day of disease In other words serum seemed to aid up to a certain point in preventing overwhelming infection but beyond this as in the mouse it was impotent (A L Bloomfield The therapeutic value of Type I antipneumococcus serum J A M A 81 1437 1923)

42 NEWBURGH L H and MINOT George R The blood pressure in pneumonia Arch Int Med 14 48 1914

There was an old tradition in medicine that primary circulatory failure was the cause of death in lobar pneumonia A drop in blood pressure in millimeters of mercury below the pulse rate expressed in beats per minute (Gibson s index) was regarded as a very bad prognostic sign and every effort was made to combat this symptom Newburgh and Minot s observations showing that low systolic pressure was not invariably of evil omen" and that systolic pressure was often higher in fatal cases than in those which recovered disposed of the idea that blood pressure measurements could be used as a basis for prognosis in pneumonia (see also Ref 43)

43 NEWBURGH L H and PORTER W T The heart muscle in pneumonia J Exper Med 22 123 1915

Newburgh and Porter perfused the hearts of dogs dead of pneumonia and concluded that the heart muscle was not functionally impaired in pneumonia since the pneumonic ventricle beat normally as soon as it received normal blood They concluded that circulatory failure was an incident in dying pneumonia patients but not a primary disturbance This work did much to change the emphasis in treatment from the circulation to the infectious process (see also Ref 42)

44 DOCHEZ A R and AVERY O T Varieties of pneumococcus and their relation to lobar pneumonia J Exper Med 21 114 1915

Dochez and Avery extended the studies of Dochez and Gillespie (Ref 40) and again found that about 75 per cent of the pneumococci from cases of pneumonia fell into three groups If these highly pathogenic strains were the same

and concentration of specific antibodies of antipneumococcic sera" Boston M & S J 189:136 1923) when he succeeded in concentrating the crude serum Later concentrated rabbit antisera largely replaced horse serum (K Goodner F L Horsfall Jr and R J Dubos Type specific antipneumococcic rabbit serum for therapeutic purposes production processing and standardization" J Immunol 33:279 1937 see also Heffron Ref 61 p 872) The whole subject is authoritatively reviewed by F T Lord and R Heffron (*Pneumonia and Serum Therapy* [New York Commonwealth Fund London Oxford University Press 1938])

49 SUTTON Alan C and SEVIER Charles E A study of the bacteremia in lobar pneumonia Bull Johns Hopkins Hosp 23:315 1917

The writers made daily quantitative blood cultures on a consecutive series of patients "Ninety three per cent of the patients with persistently negative blood cultures recovered without complication Of the patients with positive blood cultures all with over five colonies per cc at any period of the disease died except one with twenty colonies on admission who received serum therapy This work showed very clearly that bacteremia was not the cause of death but that bacteremia was an indication that the powers of resistance of the patient against infection were breaking down his immunological status in other words came to resemble that of the mouse which notably has little resistance against pneumococcus infection From these observations Bloomfield drew conclusions as to the practical efficacy of serum therapy (Ref 41) which has little curative value after increasing bacteremia is under way However it was shown later that patients even with progressive bacteremia could be saved by a powerful pneumococcidal agent such as penicillin (Ref 62) Sutton and Sevier s observations were confirmed by others (Jesse G M Bullowa and Clare Wilcox "Incidence of bacteremia in the pneumonias and its relation to mortality" Arch Int Med 55 558 1935) Important recent studies on bacteremia in pneumonia are those of O H Robertson Morton Hamburger Jr and Lucien A Gregg "On the nature of bacteremia in experimental pneumococcal pneumonia in the dog" J Exper Med 97 283 1953 Lucien A Gregg and O H Robertson J Exper Med 97 297 1953

50 HEIDELBERGER M and AVERY O T The soluble specific substance of pneumococcus J Exper Med 38 73 1923

The writers showed that the soluble specific substance formed by pneumococci (A R Dochez and O T Avery "The elaboration of specific soluble substance by pneumococcus during growth" J Exper Med 26 477 1917) consists mainly of a carbohydrate which is type specific In another paper (O T Avery and M Heidelberger "Immunological relationships of cell constituents of pneumococcus J Exper Med 38 81 1923) it was pointed out that the protein of pneumococcus exhibited only species specificity whereas the soluble substance was type specific These observations became of the greatest importance in practical work on immunity The immense literature is reviewed by White (Ref 59 pp 238 ff) but for a brief authoritative summary see Oswald T Avery The role of specific carbohydrates in pneumococcus infection and immunity Ann Int Med 6 1 1932

throat during the period of observation whereas many were persistent carriers of the same strain Carriage seemed to have no definite relation to clinical pneumonia

46 AVERY Oswald T A further study on the biological classification of pneumococci J Exper Med 22 804 1915

The original groups of pneumococci described by Dochez and Gillespie (Ref 40) were eventually found to be divisible into many more types (Ref 56) Avery s paper represented a start in this direction when he showed that at least three subgroups of pneumococcus Type II could be recognized by specific immune reactions

47 STRYKER Laura M Variations in the pneumococcus induced by growth in immune serum J Exper Med 24 49 1916

Stryker made the important observation that pneumococci grown in immune serum did not become more virulent but lost their virulence The bacteria at the same time lost their capsules and were phagocyted in normal serum Virulence and capsule could then be restored by animal passage These observations were a prelude to the discovery so important in the mechanism of pneumococcus infection that invasiveness was associated with the presence of the specific capsular substance (Ref 50) and that recovery from infection was dependent on the neutralization of this capsular substance by naturally produced immune bodies or by foreign serum (Ref 51)

48 AVERY Oswald T CHICKERING H T COLE Rufus and DOCHEZ A R Acute lobar pneumonia prevention and serum treatment Monogr Rockefeller Inst M Research No 7 1917

In this important monograph the Rockefeller workers summarize their studies on pneumonia to date The methods for isolating pneumococci and "typing them by mouse inoculation and by agglutination are described The details of preparing immune horse sera and the technique of serum therapy are given One hundred and seven cases of Type I lobar pneumonia were treated with a mortality of 7 5 per cent as against a mortality of 25-30 per cent in the same hospital before the era of serotherapy Unfortunately conditions vary so much in different places and different outbreaks that years went by without everyone being convinced of the efficacy of the serum under every circumstance It is impossible to quote all the vast literature on the subject but the material is critically analyzed in Heffron s book (Ref 61 p 880) Among 3 611 cases of Type I pneumonia for example treated in various localities the mortality varied in different groups from 4 1 to 47 per cent with over all death rates of 16 5 per cent

Since serum therapy has been entirely replaced by antibiotics the controversy as to the value of the former becomes largely of historical interest However certain landmarks should be mentioned One of the great difficulties with the early use of large quantities of unrefined horse serum was the high incidence of severe serum reactions These were described in detail by A L Bloomfield ("Effects of serum therapy in lobar pneumonia Bull Johns Hopkins Hosp 28 301 1917) and others An advance was made by L D Felton ("Isolation

on this complex subject is illustrated by the work of Austrian (Robert Austrian and Colin M MacLeod "Acquisition of M protein by pneumococci through transformation reactions" J Exper Med 89 451 1949 and Robert Austrian "Morphological variation in pneumococcus" J Exper Med 98:21 35 1953)

54 TILLETT William S and FRANCIS Thomas Jr Cutaneous reactions to the polysaccharides and proteins of pneumococcus in lobar pneumonia J Exper Med 50 687 1929

Only a few of the vast number of papers on immunity reactions can be mentioned in this bibliography but some of those having immediate clinical application should be discussed Tillett and Francis found that an intradermal injection of pneumococcus polysaccharide caused a prompt reaction of the wheal type when the patient had recovered from infection The reaction was type specific and was associated with the presence of specific antibodies in the circulating blood This skin test became an important practical guide to treatment because the development of a positive reaction indicated that recovery was under way (see also T Francis Jr and W S Tillett "Cutaneous reactions in pneumonia development of antibodies following the intradermal injection of type specific polysaccharide" J Exper Med 52:573 1930 Thomas Francis Jr "The value of the skin test with type-specific capsular polysaccharide in the serum treatment of Type I pneumococcus pneumonia J Exper Med 57:617 1933 J C Edwards C L Hoagland, and L D Thompson "Type specific polysaccharide skin test in serum therapy of pneumonia" J A M A 113:1876 1939)

55 LOSCHCKE H Untersuchungen uber die kruppose Pneumonie Beitr z. path Anat 86 201 1931

Loschcke s important studies on pathogenesis were made on human material and really preceded the experimental observations of Robertson and his group (Ref 57) Loschcke concluded that the infection of alveoli occurred not by the blood stream but by inhalation of pneumococci He thought that a "hyperergic" reaction led to outpouring of edema fluid in which pneumococci grew rapidly and that infection spread from alveolus to alveolus through the pores of Kohn and by overflow from one bronchus into another

56 COOPER Georgia ROSENSTEIN Carolyn WALTER Annabel and PEIZER Lenore The further separation of types among the pneumococci hitherto included in group IV and the development of therapeutic antisera for these types J Exper Med 55 531 1932

From the first differentiation of types of pneumococci (Refs 40 44) emphasis had been placed on the development of specific antisera Through the years the original serological groups were found to consist of more and more immunologically distinguishable types This work went on all over the world and the numerous papers are summarized in White (Ref 59 p 103) Cooper and her associates were able to describe thirty two types and antisera suitable for clinical trial were prepared for fourteen while Eddy later found that the number had risen to seventy five (B F Eddy "Nomenclature of pneumococcus types" Pub Health Rep 59 449 1944) Certain clinical associations with various types were also pointed out

51 AVERY Oswald T and HEIDELBERGER Michael Immunological relationships of cell constituents of pneumococcus (second paper) J Exper Med 42 367 1925

In this paper the writers first hinted at the concept so fundamental in practical immunology of pneumococcus infection that the soluble capsular substance of *the organisms had to do with the virulence of the infection and that specific* immune bodies dissolved or neutralized such capsular substance rendering the pneumococci vulnerable If final proof be brought for the conception that the capsular zone of the organism is largely composed of this carbohydrate sub stance is part of the defense mechanism of the cell and is the site of its initial contact with antibody then these soluble bacterial polysaccharides acquire new significance not only in the serological reactions of the cell but in the actual process of infection and immunity in the host"

It has recently been shown that highly virulent strains produce more soluble specific substance than do moderately virulent or avirulent strains (Colin M MacLeod and Marjorie R Krauss "Relation of virulence of pneumococcal strains for mice to the quantity of capsular polysaccharide formed in vitro" J Exper Med 92 1 1950 Barry Wood Jr and Mary Ruth Smith "Host parasite rela tionships in experimental pneumonia due to pneumococcus Type III" J Exper Med 92 85 1950) This work was carried forward and elaborated by im proved methods in subsequent papers (Michael Heidelberger and Oswald T Avery "The soluble specific substance of the pneumococcus (second paper) J Exper Med 40 301 1924 Michael Heidelberger Walther F Goebel and Oswald T Avery "The soluble specific substance of pneumococcus (third paper) J Exper Med 42 727 1925)

52 BARACH Alvan L Methods and results of oxygen treatment of pneu monia Arch Int Med 37 186 1926

Because of the obvious anoxemia which *is so common in* pneumonia (C Lunsgaard Anoxemia in lobar pneumonia Medicine 4 345 1925) it was hoped that oxygen administration might be a fundamentally helpful measure *in acute lobar pneumonia Barach in this paper reviews the subject* authorita tively and concludes The value of oxygen treatment is felt to be supportive and not curative Carl A L Binger s paper is also of importance (Anoxemia *in pneumonia and its relief by oxygen inhalation J Clin Investigation* 6 203 1928) The technique of oxygen administration is fully detailed in Alvan L Barach *Principles and Practice of Inhalational Therapy* (Philadelphia 1944)

53 GRIFFITH Fred The significance of pneumococcal types J Hyg 27 113 1928

In this now classical paper Griffith *presented* an elaborate study on the inter conversions of "rough" and "smooth strains of pneumococci in relation to virulance and to epidemiological problems A method of producing the "S" to R" change *is* described A great deal of work has subsequently been done on the transformation of pneumococcus types The Rockefeller group found that a nucleic acid of the desoxyribose type was concerned with the transformation of pneumococcus Type III (Oswald T Avery Colin M MacLeod and Maclyn McCarty "Studies on the chemical nature of the substance inducing transfor mation of pneumococcal types" J Exper Med 79:137 1944) Recent work

toxic effects on the optic nerves in favor of serotherapy which held sway until 1938 (H G Moore and A M Chesney "A further study of ethylhydrocuprein [Optochin] in the treatment of acute lobar pneumonia" Arch Int Med 21:659 1918) Whitby found sulfapyridine much more effective than sulfanilamide in experimental pneumococcus infection and the clinical use of the drug was soon begun The early work is reviewed in F T Lord E S Robinson and R Heffron *Chemotherapy and Serum Therapy of Pneumonia* (New York Commonwealth Fund London Oxford University Press 1940) The results were moderately satisfactory but just as in the early days of steam ships still carried some sail so sulfonamide therapy was often combined with serum The frequency of empyema and of severe nausea and vomiting with sulfapyridine was found objectionable and the whole subject was still under debate when the advent of penicillin made the drug obsolete Other sulfonamides were also tried and some of the useful papers on the whole subject are S M Evans and Wilfred F Gaisford "Treatment of pneumonia with 2 (*p* aminobenzene sulphonamido) pyridine" Lancet 2:14 1948 J M Ruegsegger N L Brokers M Hamburger and E S Grupen "The treatment of pneumococcal pneumonia with sulfapyridine" Am J M Sc 206 323 1943 H F Flippin L Schwartz and A H Domm "Modern treatment of pneumococcic pneumonia" J A M A 121 230 1943 A E Price and C B Myers "Treatment of pneumonia with sulfathiazole" Arch Int Med 70:558 1942 W S Tillett "Specific anti pneumococcal immunity in relation to the chemotherapy of pneumonia" J Clin Investigation 21 511 1942 F T Billings and W B Wood Jr "The use of sulfadiazine in the treatment of pneumococcal pneumonia" Bull Johns Hopkins Hosp 69 314 1941 M Finland F C Lowell and E Strauss "Treatment of pneumococcic pneumonias with sulfapyridine sulfathiazole and serum" Ann Int Med 14 1184 1941 Colin M MacLeod ("Chemotherapy of pneumococcic pneumonia" J A M A 113 1405 1939) discussed the mechanism of sulfonamide action in pneumonia and pointed out that sulfonamides exert a strictly bacteriostatic effect until immune bodies and the phagocytic system are sufficiently effective to extirpate the infection Thus sulfonamides and serum supplement each other in contrast to the bactericidal effect of penicillin (Ref 62) The important paper of D D Woods ("The relation of *p* amino benzoic acid to the mechanism of the action of sulphanilamide Brit J Exper Path 21 74 1940) should also be mentioned

61 HEFFRON Roderick Pneumonia with general reference to pneumococcus lobar pneumonia New York Commonwealth Fund London Oxford University Press 1939

This monumental book supplements that of White (Ref 59) and deals with every phase of lobar pneumonia There is a bibliography of 1 471 references

62 KEEFER Chester S BLAKE Francis G MARSHALL E Kennerly Jr LOCKWOOD John S and WOOD W Barry Jr Penicillin in the treatment of infections J A M A 122 1217 1943

Penicillin was soon tried in all sorts of infections In this early report Keefer and his associates stated "The pneumococcus is extremely sensitive to the action of penicillin It is plain that penicillin is another potent weapon in the treatment of pneumococcic pneumonia" This statement was based on

As one sees the typing and serotherapy of pneumococci were becoming exceedingly complex when the discovery first of sulfonamides (Ref 60) and later of penicillin (Ref 62) made them obsolete in clinical practice after dominating the field for nearly thirty years

An authoritative evaluation of the whole problem of pneumococcus types is that of Maxwell Finland "The present status of the higher types of antipneumococcus serums J A M A **120** 1294 1942

57 TERRELL Edward E ROBERTSON Oswald H and COGGESHALL Lowell T Experimental pneumococcus lobar pneumonia in the dog I Method of production and course of the disease J Clin Investigation **12** 393 1933
ROBERTSON Oswald H COGGESHALL Lowell T and TERRELL, Edward E II Pathology *ibid* p 433
ROBERTSON Oswald H COGGESHALL Lowell T and TERRELL, Edward E III Pathogenesis *ibid* p 467

There is a vast literature of speculation and experiment on the pathogenesis of lobar pneumonia which is reviewed by Heffron (Ref 61 p 232) These now classical observations of Robertson and his associates following Loschcke (Ref 55) initiated a new era because they revealed the intimate details of the lesion and demonstrated that spread of infection was carried on a peripheral wave of bacteria containing edema fluid These findings were confirmed by many workers C Loosli (The pathogenesis and pathology of experimental Type I pneumococcic pneumonia in the monkey J Exper Med **76** 79 1942) reviewed the earlier work and presented observations of his own which seem definitely to disprove former views that bacterial spread in the pneumonic lung is through the lymphatics He *supported the idea now generally accepted* that the organisms enter new alveoli through the pores of Kohn and by the bronchi.

Robertson later presented an important summary of his work Newer knowledge concerning the inception of pneumonia and its bearing on prevention Ann Int Med **18** 1 1943

58 BLAKE F G HOWARD M E and HULL W S Artificial pneumothorax in lobar pneumonia Medicine **15** 1 1936

Artificial pneumothorax had a brief but enthusiastic vogue in the therapy of lobar pneumonia The subject is reviewed in this monograph

59 WHITE Benjamin The biology of pneumococcus New York Commonwealth Fund London Oxford University Press 1938

This comprehensive book with a bibliography of nearly sixteen hundred references *deals with every phase of the biology of pneumococcus and is an invaluable* storehouse of information

60 WHITBY Lionel E H Chemotherapy of pneumococcal and other infections with 2 (p aminobenzenesulphonamido) pyridine Lancet *1 1210* 1938

The discovery of the sulfonamides initiated a new era in the chemotherapy of infections *Attempts at chemotherapy of pneumonia many years* before with quinine derivatives seemed promising but they were abandoned because of

Section 7

SCARLET FEVER

Bacteriology	Refs 5 6 10 11 15 16 27 28 29
Clinical description	Refs 1 2
Immunity reactions	Refs 14 17 20 21 22 24 25 26 30 31
Lesions	Refs 3 4
Pathogenesis	Refs 7 12, 18 19
Penicillin therapy	Ref 32
Postscarlatinal disorders	Refs 1 13
Serum therapy	Refs 8 9 23

collected reports of forty two patients of whom only six died However the paper of Tillett and his associates (William S Tillett Margaret J Cambier and James E McCormack "The treatment of lobar pneumonia and pneumococcal empyema with penicillin" Bull New York Acad Med 20 142 1944) giving details of management showed clearly the superlative effect of penicillin Among forty six patients only three (6 5 per cent) died Above all "bacteremia which occurred in 14 patients disappeared in every instance following injection of penicillin Tillett also *pointed out the value of intrapleural injections of* penicillin in pneumococcic empyema When penicillin first became available supplies were scarce and uncertain so that many cases were treated with serum sulfonamides and penicillin

Colin M MacLeod and Edna R Stone (Differences in the nature of antibacterial action of the sulfonamides and penicillin in their relation to therapy" Bull New York Acad Med 21 375 1944) point out that in contrast to sulfonamides (Ref 60) penicillin exerts a direct bactericidal effect on pneumococcus both in the test tube and in the body Thus penicillin cures without specific immunity being essential although the development of immunity is of course desirable

A recent summary of the practical use of antibiotics in pneumococcus pneumonia is that of Harry F Dowling ("Pneumococcal and streptococcal infection in Henry Welch *Principles and Practice of Antibiotic Therapy* [New York Medical Encyclopedia Inc 1954] p 295)

63 WOOD W B Jr The mechanism of recovery in acute bacterial pneumonia Ann Int Med *27 347 1944*

From the early days of the subject there has been speculation and experiment on the mechanism of recovery from lobar pneumonia and of the dramatic phenomenon of the crisis For the most part the older work attempted to link recovery with the appearance of demonstrable antibodies It has not been clear however whether all such antibodies were the cause of recovery or whether they were simply coincident (see White Ref 59 and Heffron Ref 61 for the early literature)

Wood summarizes newer views on the mechanism of recovery especially with reference to surface phagocytosis which may begin to operate in the absence of antibodies This work was presented more in detail previously (W *Barry Wood Jr Mary Ruth Smith and Barbara Watson* Studies in the mechanism of recovery in pneumococcal pneumonia IV The mechanism of phagocytosis in the absence of antibody" J Exper Med 84 387 1946) and was later *summarized with full bibliography* (W Barry *Wood Jr* "Studies on the cellular immunology of acute bacterial infections Harvey Lect 1951-52 [New York Academic Press Inc 1953] p 72)

urine is scanty "There is no doubt of the unusual colour being occasioned by the red matter of the blood" "There is another part of the blood which I have almost always found present in the urine of persons affected with this dropsy which is serum"

On the whole however this is a primitive account and there is no speculation as to the cause or nature of the trouble But by 1861 W Hamburger ("Ein Beitrag zur Lehre und zur Therapie des Brightschen Scharlachhydrops" Vrtljschr prakt Heilk 1:24 1861) was thinking critically on the subject He did not believe that nephritis was caused by the rash because nephritis is absent after other exanthemata such as measles or smallpox He did not think exposure to cold an adequate explanation nephritis might occur in the most carefully safeguarded children and not in those who "ran around barefooted" He pointed out the difference in frequency of nephritis in different epidemics and he noted that nephritis might follow the mildest case and that indeed Bright's disease not preceded by recognized scarlet fever might still result from the same cause He recognized as other postscarlatinal effects lymphadenopathy and acute articular rheumatism His speculations on the exact cause are however meaningless to the modern reader and it remained for Schick to introduce the concept of a hypersensitive reaction (Ref 13)

2. TROUSSEAU A Clinique médicale de l'Hôtel Dieu de Paris 1:1 Scarlatine Paris 1861

It is impossible to attribute to any one man the first adequate clinical description of scarlet fever The pre nineteenth-century accounts of Sydenham of Fothergill of Huxham and of others are often referred to but one finds them quite inadequate What may have been scarlet fever was confused with throat infections such as diphtheria and possibly with various other "ulcerous" sore throats the rashes of scarlet fever of measles and perhaps of pandemic influenza were not clearly distinguished In some accounts sore throat is not mentioned at all the classification of simple anginose and malignant forms of scarlet fever was for a long time popular The severity of outbreaks varied and the incidence of combined infections such as scarlatina and diphtheria and of violent secondary mixed infections must have been frequent Furthermore many accounts are diluted by lengthy dissertations on the weather the winds the prevalence of other disease and all sorts of extraneous matter Or the observer is distracted by lengthy discussions of the appearance of the urine the character of the sweats etc Finally the emotional overlay on the part of the physicians and parents helpless in the face of what was often a disease terrifying in its malignancy made unbiased reporting difficult [1] It was only gradually therefore that adequate accounts with good descriptions of the throat and of the rash and with clear definitions of the course of the disease and its complications emerged

[1] "So fatal have been the results so fearful the ravages so widespread the devastation of the disease so interesting the period of life at which it commonly occurs just as parental hopes are budding with promise and the tendrils of affection entwining themselves most closely round the heart that the very name is a signal of distress and its introduction into the family circle is looked upon as the angel of death with an irreprievable warrant to destroy" (Casper Morris *Lectures on Scarlet Fever* [Philadelphia Lindsay & Blakiston 1851] p 1)

Section 7

SCARLET FEVER

IN FOLLOWING the tangled thread of increasing knowledge through the vast literature on scarlet fever the reader should remember that the main problems which have caused so much confusion in the past have now been solved If the earlier students of the disease had stuck to their guns when they proposed first that the rash of scarlet fever is due to a soluble toxin produced in the throat by the causal organisms and second that a permanent immunity to the rash toxin is usually conferred by an attack without lessening susceptibility to subsequent infection with the same types of hemolytic streptococci many of the puzzles which later perplexed the most astute observers would have been resolved

It will not be profitable to attempt to define the origins of the obviously descriptive terms scarlet fever and "scarlatina An excellent discussion of the problem is to be found in the book by J D Rolleston (*The History of the Acute Exanthemata* [London William Heinemann 1937] p 47) who points out that these designations were already in common use in the seventeenth and eighteenth centuries My little girl Susan is fallen sick of the meazles we fear or at least of a scarlett feavour said Samuel Pepys in his diary under the entry for November 10 1664

Aside from the *Index Medicus* and the *Index Catalogue* of the Surgeon General s Library extensive bibliographies may be found in the following

ESCHERICH, T and SCHICK B *Der Scharlach* (Vienna Alfred Holder 1912) especially the older literature

Annals of the Pickett Thomson Research Laboratory (London Baillière Tindall & Cox 1924–25) 1 115 v 6 (1930)

WILLIAMS ANNA W *Streptococci in Relation to Man in Health and Disease* (Baltimore Williams & Wilkins Co 1932) chapter on scarlet fever p 125 and Bibliography p 221

RANTZ LOWELL A *The Prevention of Rheumatic Fever* (Springfield Ill Charles C Thomas 1952) recent literature

1 WELLS William Charles Observations on the dropsy which succeeds scarlet fever Tr Soc Improvement M & Chir Knowledge 3 167 1812

Although the dropsy following scarlet fever was mentioned in seventeenth and eighteenth century accounts the first useful description in English was that of Wells Its first appearance is generally on the twenty second or twenty third day after the commencement of the preceding fever If I can trust however to the report of a careful mother it may come as early as the sixteenth day and I know from my own observations that its attack may be delayed to the twenty fifth When it has not appeared before the end of the fourth week I have always ventured to affirm that its attack was no longer to be dreaded" Contrary to what might have been expected the dropsy often comes on after a very mild fever and when the person who had suffered it appeared to have nearly or altogether recovered his former health" "In the beginning of the disease the

3 HEUBNER Otto Beobachtungen uber Scharlachdiphtherie Jahrb f Kinderh 14:1 1879

At a time when the throat lesions of scarlet fever and diphtheria were badly confused Heubner made histological studies of the tonsils from patients with what appeared to be uncomplicated scarlet fever who died in the first few days of the disease Scarlatinal diphtheria is intimately bound up with the entire disease—scarlet fever—and is to be sharply differentiated both clinically and histologically from primary diphtheria "

4 NEUMANN I Ueber die histologischen Veranderungen der Haut bei Morbillen und Scharlach (Wiener) Med Jahrb p 159 1882

This appears to have been the first attempt at a systematic biopsy study of the skin in scarlet fever The main findings were hyperemia edema extravasations of blood cells and some inflammatory cells Details as to day of disease on which the specimens were obtained are lacking P G Unna (*Die Histopathologie der Hautkrankheiten* [Berlin A Hirschwald 1894] p 628) also emphasized the immense dilation of the blood vessels with only a few inflammatory cells E Rach later (Beitr path Anat 47:455 1910) amplified the earlier observations He emphasized hyperemia exudate into the superficial skin layers the collection of the exudate into tiny vesicles and finally death of epithelium with desquamation He regarded the process as toxic rather than inflammatory in the classical sense

5 LOEFFLER Friedrich Untersuchungen uber die Bedeutung der Mikro-Organismen fur die Entstehung der Diphtherie beim Menschen bei der Taube und beim Kalbe Mitt a d k Gsndhtsamte 2:421 1884

The relationship of streptococci to disease as well as the occurrence of these organisms in healthy people was recognized early in the bacteriological era so that in the 1880 s there was already a huge literature on the subject By that time streptococci had been isolated from erysipelas puerperal fever and scarlet fever It is extremely difficult to assign priority Those interested in pursuing details may scan the *Index Catalogue* of the Surgeon General s Library in which up to 1910 there are some seventy closely printed pages of references to scarlet fever alone Most of the findings in the early papers are confused by inadequate methods of isolation mixed infection difficulties in classification etc For example Hallier (Der pflanzliche Organismus im Blute der Scharlach kranken" Jahrb f Kinderh 2 169 1869) has been credited with being the first to isolate streptococci from the blood of scarlet fever patients An examination of his paper however shows that he was dealing with a mold his drawings are quite conclusive they show hyphae conidia etc [2]

Loeffler in a monumental paper primarily on diphtheria seems to have been the first definitely to isolate pyogenic streptococci from cases of scarlet fever In a number of cultures of "diphtheria complicated by scarlet fever he clearly describes chains of cocci which can be seen penetrating from the necrotic sur

To show how important is examination of original reports in establishing priority Pohl Pincus (Centralbl f d med Wissensch 21 640 1883) has been spoken of in the literature as the first to describe streptococci in scarlet fever Actually he examined desquamated skin by direct smears and described cocci which in all probability were staphylococci There is no evidence that he identified streptococci

It is Trousseau *the master clinician* who *gives the first account of scarlet fever in the modern sense stripped of emotional overlay and inconsequential verbiage He points out the great differences in severity of various outbreaks* Scarlet fever may not appear on the skin it is not less serious on this account " The complications are varied and unpredictable in contrast to measles He quotes a case to show that the incubation period may be as brief as 24 hours There are minutely accurate descriptions of the character and course of the rash and of the sore throat From the first day of the disease the palate is red like the skin and the tonsils are swollen and violaceous There appear on the tonsils little white spots They are different from the false membrane of diphtheria They are pultaceous and appear to be the secretions from the surface of the [tonsillar] ulcers As the rash fades the tonsils get rid of these [white] patches although they remain reddened and sometimes ulcerated the disease is cured *Trousseau clearly distinguishes the peeling of scarlet fever from the branlike desquamation of measles In contrast to diphtheria "scarlatina does* not like the larynx There is an accurate description of the postscarlatinal disorders "I cannot repeat too emphatically that in scarlet fever one cannot consider the patients cured until a long time after the cessation of all morbid phenomena He emphasizes anasarca This accident occurs in convalescents not only if they have been exposed to cold or have committed some imprudence but even when they have remained quiet with the best of care and the most constant solicitude The associated hematuria and albuminuria are discussed Trousseau differentiates the usual postscarlatinal rheumatism" pleurisy pericarditis and endocarditis *from the occasional suppurative lesions* He points out *that it is rare for children who have had attacks of "acute articular rheumatism" to escape a later attack of the dance of Saint Guy (chorea)*

Trousseau came very near to understanding the implications of scarlatina without rash *I have seen members of the same family who having had the* sore throat without eruption were then immune to scarlet fever even though the others around them were more or less violently attacked [with scarlet fever] A child returned from school where there was an outbreak of scarlet fever she had sore throat and headache and could hardly swallow The next day the tonsils were swollen but there was no trace of skin rash Before this child was well scarlatina attacked her two sisters and father The two sisters had the rash and later peeled the father had only a few pink specks on his skin and did not peel In another family three children were sick with scarlet fever Two adult servants were attacked with violent tonsillitis but there was no exanthem Trousseau credits Graves with describing anasarca following subclinical scarlatina indicated only by overt attacks in other members of the family "These passages prove therefore that under the skies of Dublin as under the *skies of Paris the same things are manifest*

Trousseau s discussion of treatment is of less interest to the modern student but on the whole little has been added to this admirable description which *occupies some thirty closely printed pages and should be read by every student* of communicable disease *if possible in the original (translation A Trousseau Lectures on Clinical Medicine* [Philadelphia Lindsay & Blakiston 1869] 2 183)

of certain known toxins" (3) "In puerperal or in wound scarlatina the strepto cocci grow in the uterus or in the wound"

Reasons supporting these statements are given and the identity of acute streptococcal tonsillitis and scarlet fever except for the rash is pointed out Bergé's final sentence shows him to have been many years ahead of his time "As to the immunity conferred by scarlatina it exists only against the rash because the tonsillitis on the contrary recurs frequently after scarlet fever"

Had later workers appreciated these findings much useless labor would have been saved Indeed this point of view seems to have been "in the air" in the nineties A Baginsky for example raises the question of whether scarlet fever was not caused by cocci "which had the ability when growing in a limited focus in the pharynx to flood the body with a toxin which by the hematogenous route brings out on the skin the scarlatinal exanthem" ("Zur Aetiologie der Diphtherie" Berl klin Wchnschr 29 183 1892) Numerous other writers in the succeeding ten years came to similar conclusions and the literature to date is summarized by G Gabritschewsky (Ueber Streptococcenerytheme und ihre Beziehung zum Scharlach" Berl klin Wchnschr 44–1 556 1907) Many contemporary writers also stated their unequivocal belief that streptococci were the cause of scarlet fever on the basis of the constant presence of these bacteria in the throat in the disease response to specific serum therapy and production of a rash by scarlatinal streptococcal vaccine (Gabritschewsky Centralbl f Bakt 41 844 1906) It was Jochmann's influence (Ref 12) which weighed against this view

8 MARMOREK Alexandre Le Streptocoque et le sérum antistreptococcique Ann Inst Pasteur 9 593 1895

Although work was already being done on the differentiation and virulence of streptococci attempts at preparing immune sera against these bacteria had been rudimentary and had concerned mainly small laboratory animals Marmorek made important observations on the growth and virulence of streptococci he concluded that strains from human disease were all of one sort and that streptococci of erysipelas for example were not the specific cause of the disease to be sharply differentiated from pyogenic streptococci obtained from an abscess He thought that the type of disease produced depended on portal of entry and virulence All this is of interest in view of the claims made many years later that the streptococci of scarlet fever and of erysipelas were immunologically distinct (Refs 10 16) which in the end (Ref 29) turned out to be incorrect Marmorek immunized large animals including horses with increasing amounts of living virulent streptococci The procedure required six months to a year A pony for example received thirteen injections comprising about 195 cc of culture over a period of five months The serum was used therapeutically in all sorts of streptococcal infections including scarlatina The results were encouraging but not conclusive Temperature often fell quicky toxic symptoms were abated, and in small animals definite protective effects were obtained These results seem much like those described by Blake with Dochez's serum thirty years later (Ref 23)

Marmorek concluded this pioneer paper as follows "We are not unaware of how much caution is necessary in judging a new remedy We must beware of hasty conclusions We have exposed the facts and doctors may be anxious to

faces into the lymphatics of the tonsils Cultures in meat infusion peptone gelatin yielded colonies of long chained streptococci From the internal organs of fatal cases these organisms were also readily obtained in pure cultures which produced suppuration especially in joints when injected into rabbits and other animals Loeffler s precise and convincing work is in sharp contrast to that of most contemporaneous observers his success was due to his excellent methods and technique The whole position was well summarized by Escherich (Centralbl f Bakt 1 381 1887) From this time on no competent observer doubted the frequent or constant occurrence of streptococci in scarlet fever The questions debated were whether these organisms were the primary cause of the disease secondary invaders or incidental findings of no consequence at all Obviously these questions could not be finally answered until better methods of isolating and classifying streptococci were developed (see Refs 15 18 28 29) which showed that cultures properly made from the pharynx early in scarlet fever yield *hemolytic* streptococci in every case (Ref 16)

6 The relation between milk scarlatina in the human subject and disease in the cow Report of Mr W H Power and of Dr Klein to the Local Government Board entitled Milk scarlatina in London 1885" Practitioner 37 61 143 1886

Another important link in the chain of evidence incriminating streptococcal infection as a cause of scarlet fever came from observations on so called milk scarlatina The literature especially from England of the last quarter of the century is full of reports of outbreaks of the disease which seem clearly related to ingestion of milk It was Power however who in this classical study definitely traced an outbreak in London through the retailer in South Marylebone to a particular cow in the dairy farm supplying the milk This is a brilliant example of public health "detective work and should rank as a classic with Budd s observations on typhoid fever Study of the lesions of the diseased udders by Dr Klein yielded in culture micrococci arranged as diplococci and as shorter or longer chains—streptococcus—these latter sometimes of great length" "The milk during the act of milking is pretty sure to become contaminated The organisms would find in the milk a good medium in which to multiply Such milk would then practically correspond to an artificial culture of streptococcus such as we have found capable of setting up a general disease when inoculated subcutaneously into calves The description of the animal lesions are of interest it was noted for example that "sections through the kidney showed well marked glomerulonephritis

7 BERGE André Sur la pathogénie de la scarlatine Compt rend Soc de biol 5 1012 1893

When Dochez and the Dicks thirty years later described the local growth of streptococci in the throat with production of a soluble toxin not enough credit was given to the precise observations of Bergé whose conclusions were as follows

(1) "Scarlet fever is a local infection (2) The infectious agent which causes it is a streptococcus in ordinary scarlatina the streptococcus grows in the crypts of the tonsils where it secretes an erythemogenic toxin the diffusion of which into the organism produces the exanthem and enanthem after the manner

subject is that of Bela Schick ("Ueber die weiteren Erfolge der Serumbehandlung des Scharlach" Deutsche med Wchnschr 31 2092 1905) and later that of Escherich and Schick (*Der Scharlach* [Vienna Alfred Holder 1912])

10 MOSER Paul and VON PIRQUET C Agglutination von Streptococcen durch Pferdeserum Wien klin Wchnschr 15:1086 1902

These were the first systematic attempts to define scarlatinal streptococci as a group The authors found that antisera prepared against scarlatinal streptococci agglutinated any strain isolated from the blood of scarlet fever patients in as high titer as the homologous strain but streptococci from other sources were agglutinated in no higher titer than with normal horse serum Antisera prepared from non scarlatinal strains did not agglutinate scarlatinal streptococci in high titer Moser and Von Pirquet found in brief what Dochez observed nearly twenty years later (Ref 15) F Neufeld ("Ueber Immunitat und Agglutination bei Streptococcen" Ztschr f Hyg u Infektionskr 44 161 1903) a very reliable worker was however unable to confirm Moser s work He found that *antistreptococcal rabbit sera had a specific agglutinating effect against the homologous scarlatinal strain* but that they agglutinated streptococci from various sources equally well G H Weaver ("Agglutination of streptococci especially those cultivated from cases of scarlatina by human sera" J Infect Dis 1:91 1904) also pointed out the technical difficulties in this sort of work and concluded "The agglutination reaction between the streptococci cultivated from cases of scarlatina and the serum from cases of scarlet fever is in no way specific"

It is of interest that years later this whole dispute was repeated with the same outcome (Refs 15 16 28 29)

11 SCHOTTMULLER H Die Artunterscheidung der fur den Menschen pathogenen Streptococcen durch Blutagar Munchen med Wchnschr 50 849 1903

Schottmuller had introduced the technique of blood culture in 1897 and soon found that the appearance of colonies on blood agar plates might be of diagnostic value He found that colonies of pathogenic streptococci showed a "characteristic circular light area around them This light area which results from the complete absorption of the hemoglobin has an area of 2–3 mm" Schottmuller clearly distinguished the green producing non hemolytic streptococci and gave them the designation *mitior seu viridans* He never found the latter type in scarlet fever or in pyogenic processes He did not realize however that S *viridans* is the most important constituent of the normal basic flora of the upper air passages

This work was of fundamental importance and really was the start of a useful subdivision of streptococci (Ref 15) It was elaborated years later by J Howard Brown in his monograph (*Use of Blood Agar for Study of Streptococci* [Monogr No 9] [New York Rockefeller Institute for Medical Research 1919])

12 JOCHMANN G Die Bacterienbefunde bei Scharlach und ihre Bedeutung fur den Krankheitsprocess Ztschr f klin Med 56 316 1905

This long and well reasoned discussion by a recognized authority on infectious disease brought to a head the controversy as to whether streptococci were the

use this serum This has not yet reached the point of efficiency we hope for At any rate let doctors not forget the necessity of a bacteriological diagnosis with out which they expose themselves to serious mistakes These observations are amplified in another paper "Traitement de la scarlatine par le sérum antistrep tococcique" *ibid* 10 47 1896

Marmorek immunized his animals with whole broth cultures It has been pointed out that his sera may therefore have had both antitoxic and antibacterial potency which might explain the excellent prompt effects which he achieved in some cases

Attempts at serum therapy have played such a great part in elucidating the problems of scarlet fever that this paper and those subsequently listed (Ref 9) on the same subject are especially important

9 MOSER Paul Ueber die Behandlung des Scharlachs mit einem Scharlach Streptococcenserum Wien klin Wchnschr 15 1053 1902

Moser was unable to obtain good results with Marmorek s serum (Ref 8) Thinking this might be due to differences in the infecting strains he immunized horses with "many strains" of scarlatinal streptococci using a mixture of living cultures "Since clinical observation of scarlet fever revealed signs not only of infection but also of intoxication we presumed that a specific streptococcus serum might influence both infection and intoxication Moser gave 30–180 cc usually in one dose subcutaneously apparently without much consequent serum sickness He found that if the serum was given early in the disease there was especially in severe cases remarkable improvement in well being suppres sion of rash or rapid fading fall of temperature and pulse rate and clearing of toxic symptoms As one reads the results they are certainly impressive Moser was less sure that pyogenic or postscarlatinal complications were prevented or altered On the basis of these results he raised the question of whether strepto cocci are not the real cause of scarlet fever and not just a combination with an unknown agent He also felt with Von Pirquet that scarlatinal streptococci were a special group and were agglutinated by immune sera in an entirely different way from other streptococci

Moser s work is just as impressive as that of Blake using Dochez s serum many years later (Ref 23) Why then did antiscarlatinal sera after extensive trials between 1895 and 1905 fall largely into disuse in subsequent years until revived by Dochez and the Dicks (Ref 20)? First of all it was difficult to standardize the sera and as the beneficial effect was undoubtedly due mainly to neutralization of soluble toxins antisera against strains which were not good toxin producers would be useless Horses also vary in their response to immuni zation In some cases perhaps too little serum was used Hence the clinical results were so variable as not to be convincing to all Furthermore the in fluential paper of Jochmann (Ref 12) in which he definitely concluded that streptococci were not the cause of scarlet fever discouraged further attempts Thus Osler in 1910 (*Principles and Practice of Medicine* [7th ed New York D Appleton & Co 1910] p 140) at the end of his article on scarlet fever has a brief paragraph on serum treatment in which he simply states that it has been used in Europe but he does not advise it

A critical and comprehensive review of the contemporary literature on the

of the original antigen which could participate in an antigen antibody reaction to produce a toxic agent

The most modern point of view is really only an elaboration of Schick s ideas Some have invoked the notion that a reinfection with a different type of hemolytic streptococcus may furnish the antigen for a reaction as a result of sensitization in the original illness to products of streptococcal metabolism (see L. A Rantz, P J Boisvert and W W Spink "Hemolytic streptococcus sore throat the post streptococcic state" Arch Int Med 79:401 1947)

14 SCHULTZ, W and CHARLTON W Serologische Beobachtungen am Scharlachexanthem Ztschr f Kinderh **17** 328 1918

The Schultz Charlton rash extinction test became an invaluable tool in studying the immunology of scarlet fever Schultz and Charlton showed that both convalescent scarlatinal serum and normal serum injected intradermally (1 0 cc) blanched the rash The blanching began in about 5–6 hours and persisted throughout the illness in contrast to that produced by epinephrine which began within a minute or two and disappeared in 5–6 hours Schultz and Charlton concluded therefore that their reaction was not due to simple vasoconstriction Furthermore convalescent serum drawn on various days gave a negative test up to the fourteenth day when positives began to appear all sera from the nineteenth day on extinguished the rash Schultz and Charlton had no idea as to the cause of this phenomenon which was later shown to be due to neutralization of erythrogenic toxin by specific antitoxin (Refs 17 20 26) K. Birkhaug (J Clin Investigation **1** 273 1925) reviews the contemporary literature on the Schultz Charlton test and adds observations of his own He found that neither convalescent nor normal sera blanched the rash if it had been present over 2–3 days Dochez s antiscarlatinal horse serum was highly effective

15 DOCHEZ A R AVERY O T and LANCEFIELD R C Studies on the biology of streptococcus I Antigenic relationships between strains of Streptococcus hemolyticus J Exper Med **30** 179 1919

Dochez and Avery had concluded their work on pneumococcic types (Monogr Rockefeller Inst M Research," No 7 [October 16 1917]) and it was natural for them to embark on similar studies of streptococci Hemolytic streptococci from human sources were shown by agglutination reactions with immune sera prepared in animals and by protection tests to fall into at least four biological types

It was these observations which led Dochez and his associates to attempt to find out whether the streptococci of scarlet fever fell into a uniform immunological group hence it must be regarded as an important landmark in the subject The improved technique used by these workers seemed to promise more definite results than the inconclusive attempts previously made to answer this question (Ref 10)

16 BLISS Walter P A biological study of hemolytic streptococci from the throats of patients suffering from scarlet fever Preliminary report Bull Johns Hopkins Hosp **31** 173 1920

Attempts at serological classification of streptococci from cases of scarlatina had been made years earlier with variable success (Ref 10) Bliss following Do-

primary cause of scarlet fever Jochmann critically reviewed the extensive litera ture pro and con and added observations of his own His final conclusion was that streptococcus was not the primary cause but was responsible for septic complications His reasons were that scarlet fever patients who died of septic complications after a week or more of the disease almost all had streptococci in the blood whereas streptococci were conspicuously absent in the hyperacute cases who died within one to three days after onset "Here the scarlatinal poison unfolds its pure effect before streptococci have become operative He also noted that streptococci are rarely cultivated from the blood during the first few days of the disease and he could not explain the immunity conferred by an attack of scarlatina in contrast to the well known susceptibility to repeated streptococcal infections He also believed that there was nothing specific about the streptococci of scarlet fever but thought that they could produce ordinary pyogenic infections in other situations

Jochmann was an extraordinarily astute observer and thinker Most of the points which to him were evidence against a streptococcal etiology are now readily explained He was keen enough to see that scarlet fever in its early days was a highly specific disease and not a suppurative process in the strict sense he concluded that if the septic stage obviously different was due to strepto cocci there must be some other cause for the primary disease This is not far from the truth since the soluble toxin plays a prominent part in the early phe nomena while the later septic features are now known often to be due to a different streptococcus from the original strain (Ref 27) Jochmann could not understand the surprising therapeutic effects sometimes achieved with Moser s serum "In hypertoxic cases with high fever somnolence green diarrhea feeble pulse etc temperature falls within 4–12 hours after injection and the children wake up as from a sleep However suppurative complications come later so that the serum has no effect on these or on the postscarlatinal after illness" The answer of course was that Moser s serum prepared by injection of broth cul tures of streptococci had the same antitoxic effects which the Dicks demon strated twenty five years later (Ref 20)

At any rate on the strength of Jochmann s prestige the idea that strepto coccus did more than cause the complications of scarlet fever was pretty much abandoned until the work of Dochez created a new impetus (Ref 15)

13 SCHICK B Die Nachkrankheiten des Scharlach Jahrb f Kinderh 1907 Erganzungsband p 132

There is an immense late nineteenth century literature on postscarlatinal dis orders It remained for Schick however as a result of his work with Von Pirquet on serum sickness (*Die Serumkrankheit* [Leipzig and Vienna F Deuticke 1905]) to sense the resemblance to an allergic reaction and to suggest a hyper sensitive state as an explanation of scarlatinal after sickness" Schick clearly differentiated the renal lesions of early scarlet fever from postscarlatinal nephri tis He realized that in the asymptomatic interval lay the clue to the nature of the process He pointed out that the components of the postscarlatinal syn drome were probably all the results of some common cause He included fever lymphadenitis nephritis rheumatism and endocarditis He thought that altered reactivity was associated with a flareup of the original "contagium" If one reasoned in terms of serum sickness it was necessary to assume the presence

due to the fact that antitoxin has not yet developed the presence of antitoxin in "normals" is due to a previous attack perhaps subclinical of scarlet fever Variations in degree of blanching are due to differences in amount of toxin in the skin and of antitoxin in the test serum Mair by examining serum drawn early in the disease as well as convalescent serum from the same person demonstrated the development of antitoxin as the infection progressed The work of the Dicks (Ref 20) was predicted in Mair s concluding statement "It seems highly probable that the causal micro-organism will be capable of producing a toxin and by immunization of animals an antitoxin of which the latter should give the Schultz Charlton reaction in man

18 DICK George F and DICK Gladys Henry The etiology of scarlet fever J A M A 82:301 1924

The Dicks swabbed the tonsils of two volunteers with a 48-hour culture of hemolytic streptococcus isolated from the throat of a scarlet fever patient One volunteer remained well the other developed typical scarlet fever with sore throat fever leukocytosis rash desquamation etc The authors concluded "Since the streptococci used in these experiments have fulfilled the requirements of Koch s laws it may be concluded that they cause scarlet fever"

While the Dicks deserve credit for the final proof that streptococcus is the cause of scarlet fever we believe that the logical progressive and systematic approach to the problem by Dochez and his associates was equally important (Ref 19) In their paper of 1921 entitled Experimental inoculations in scarlet fever" (J A M A 77:782) the Dicks concluded "The thirty streptococcus throat inoculation experiments constitute a series large enough to discourage further experiments of the same kind with hemolytic streptococci" Seven of their volunteers developed sore throat *but no rash* the Dicks did not seem to sense at the time that these people were simply immune to the rash toxin The Dicks also did inoculations with "a pleomorphic organism similar to those previously found in cultures of throat, blood and urine in early uncomplicated scarlet fever" and although they did not produce frank disease they definitely rated it as a possible causal agent "If the pleomorphic organism bears an etiological relation to scarlet fever it should be possible by inoculation of a larger series of volunteers to produce a rash on the skin as well as the palate" This pleomorphic organism is heard of no more in the writings of the Dicks but in another paper ("Experimental scarlet fever" J A M A 81:1166 1923) they described the inoculation of five volunteers whose tonsils were swabbed with a culture of hemolytic streptococcus obtained from the "sore finger" of a woman with scarlet fever Three of these volunteers remained well one developed tonsillitis but no skin rash and one had scarlet fever with a typical rash etc Somewhat similar results were obtained in a second series of inoculations However the situation was still not clear to the Dicks who concluded "The two cases of experimental scarlet fever reported were probably caused by the hemolytic streptococcus or by some unrecognized organism closely associated with it in cultures These experiments do not justify the conclusion that all cases of scarlet fever are caused by the hemolytic streptococcus described" Their final experiment was done at a time when all thoughtful students of the subject were already convinced that the hemolytic streptococcus was the primary cause of scarlatina

chez's work (Ref 15) found that about 80 per cent of strains of hemolytic streptococcus from the throats of scarlet fever patients in the first week of the disease were agglutinated by four different antistreptococcic sera made from similar organisms but none were agglutinated by antistreptococcal sera of non scarlatinal origin except in rare cases Bliss later amplified these studies ("Studies on the biology of streptococcus" J Exper Med 36:575 1922) Although he noted various exceptions and differences in carbohydrate fermentation among the scarlatinal strains he definitely concluded that the streptococci from scarlet fever comprised a specific type Future work was to show his view to be incorrect but it furnished a tremendous stimulus to studies of the etiology of scarlet fever including the definitive human inoculation experiments of the Dicks

Other workers at the same time using similar methods came to the conclusion that scarlatinal streptococci fell into a distinct group (cf R Tunnicliff "Specific nature of the hemolytic streptococcus of scarlet fever" J A M A 74 1386 1920 Further studies on the specificity of streptococci" *ibid* 75 1339 1921 *Observations on the spread and persistence of the hemolytic* streptococci peculiar to scarlet fever J Infect Dis 29 91 1921) Tunnicliff observed that the strains obtained during convalescence and in complicating lesions were often different from those isolated during the acute phase She also found that persons associated with scarlet fever patients may develop tonsillitis without an exanthem and may harbor streptococci which belong to the same biologic group as those isolated from typical cases of scarlet fever M H Gordon ("A serological study of haemolytic streptococci Brit M J 1 632 1921) also *concluded using similar methods that scarlatinal streptococci fell into a sero*logically distinct group F A Stevens and A R Dochez as late as 1926 in an elaborate study ("Antigenic relationship between strains of streptococci from scarlet fever and erysipelas J Exper Med 43 379 1926) *still maintained* that scarlatinal and erysipelas streptococci fell into essentially different immunological groups This position was however already being questioned by the Dicks (Ref 18) by A W Williams H D Hussey and E J Banzhof ("Culture filtrates of hemolytic streptococci from scarlet fever intracutaneous reactions in test animals Proc Soc Exper Biol & Med 21 291 1924) and by British workers (J Smith The serological classification of haemolytic streptococci obtained from cases of scarlet fever" J Hyg 25 165 1926 Fred Griffith "Types of haemolytic streptococci in relation to scarlet fever" J Hyg 25 385 1926 and G R James "The relationship of streptococci to scarlet fever" J Hyg 25 415 1926)

The unraveling of this problem was confused by the fact that in a certain locality most cases of scarlet fever may for a season be caused by one predominant type It was when scarlatinal strains from various countries were compared that lack of identity was readily made out by Griffith typing (Ref 29)

17 MAIR W An immunity reaction in scarlet fever Lancet 2:1390 1923

In this extremely important paper Mair discusses the immunological problems posed by the Schultz Charlton test (Ref 14) He points out that the facts can be explained only on the basis of neutralization by antitoxin of a toxin which produces the rash Negative reactions with sera drawn early in the disease are

toxic filtrate of cultures More detailed reports on preventive immunization by injections of toxin were reported in a further paper ("The prevention of scarlet fever" *ibid.* 83:84 1924) and soon a report appeared ("Therapeutic results with concentrated scarlet fever antitoxin" *ibid* 84 803 1925) in which the Dicks described the use of their horse serum in clinical cases They concluded that the antitoxin blanches the rash[6] lowers temperatures and improves the general condition of many scarlet fever patients If given early the course of the disease was shortened and the incidence of complications and sequelae was greatly reduced The careful production of this serum its concentration and standardization so that only small amounts of horse serum needed to be injected constituted an important advance in therapy Unfortunately it was ultimately shown that the antitoxin acted mainly on the rash and perhaps certain toxic symptoms but did not have the antibacterial action necessary to eliminate the streptococcal infection it did not furnish a complete cure of the disease

Finally all the work described above was amplified in two further papers by the Dicks ("Results with the skin test for susceptibility to scarlet fever" J A M A 84:1477 1925 and "Therapeutic results with concentrated scarlet fever antitoxin" ibid 85:1693 1925) Important points were that not all strains of scarlet fever streptococci were equally good "toxin" producers the Dicks also failed to substantiate the immunological identity of scarlet fever streptococci as observed by Dochez and his associates (Ref 16) Sheep immunized with two strains of streptococci which had produced experimental scarlet fever yielded sera which agglutinated the homologous organism in high concentration but gave no cross agglutination This position was later confirmed (Ref 29)

The fundamental importance of all this work is not to be underestimated It brought clearly into focus the question of what part of the disease was due to the soluble toxin and what part was the result of the local streptococcal infection in the throat Does the soluble toxin do more than cause the rash? Is it also responsible for part or all of the toxic symptoms? Or do its effects vary in different cases? Be this as it may the applications of the toxin and antitoxin of the Dicks in immunization and in therapy has gradually fallen into some disuse partly because there may be severe reactions from the material and partly because the effects are thought to be mainly against the erythrogenic toxin—the rash Furthermore modern antibiotics are highly effective in extirpating the infection The antitoxin may still be useful however in certain patients such as very severe intensely prostrated cases in which the action of toxin may be predominant

21 KIRKBRIDE Mary B and WHEELER Mary W Comparison of reaction in individuals to toxins prepared from three strains of scarlet fever streptococci Proc Soc Exper Biol & Med 26 85 1924

Using toxins prepared from three scarlatinal strains of streptococcus the writers found that most people reacted similarly with skin tests to all three A few people failed to give a response to one or another "toxin" This suggested that not all these "toxins" were identical and that immunity might exist

[6] As predicted by Mair (Ref 17)

19 DOCHEZ A R and SHERMAN Lillian The significance of *Streptococcus hemolyticus in scarlet fever* J A M A 82 542 1924

Although his paper appeared three weeks after that of the Dicks (Ref 18) Dochez seems to deserve equal credit for establishing the streptococcus as the cause of scarlet fever He concluded From the results detailed it would seem that a specific streptococcus is the cause of scarlet fever that the disease in its principal characteristics resembles diphtheria and that both immunity in human beings and the experimental immunity developed by inoculation of animals are antitoxic in nature [3] Dochez's views were based on the consistent isolation of hemolytic streptococcus from the throat during the first days of the disease the fact that the organisms seemed to fall into a single immunological group the production in guinea pigs with this streptococcus of a disease resembling scarlet fever and the development of an immune serum[4] in the horse which "possesses the capacity to blanch the rash locally in scarlet fever and which when used therapeutically causes a marked abatement of all the symptoms

20 DICK George F and DICK Gladys Henry A skin test for susceptibility to scarlet fever J A M A 82 265 1924

The observations of the Dicks on soluble toxins in scarlet fever were of fundamental importance in leading to the final understanding of the disease Simultaneously with their work Dochez expressed the view (Ref 19) that the principal localization of the infection is in the throat in most instances and that there the streptococcus in question elaborates a toxin which is absorbed and produces the rash and general symptoms" It was the Dicks however who first prepared a usable "toxin from filtrates of cultures of streptococci obtained from scarlet fever patients they showed that an intracutaneous injection of this filtrate practically never produced a skin reaction in people convalescent from scarlet fever or with a history of a previous attack whereas 41 6 per cent of persons who had no history of scarlet fever showed a red area up to 5 cm in diameter in 24–36 hours These positive tests could be inhibited by convalescent scarlet fever serum and positive skin tests were reversed after an attack of scarlet fever This was the basis of the Dick test

The Dicks raised the question of whether all the symptoms of scarlet fever could be due to this "toxin They injected "toxin into healthy people who had never had scarlet fever (Scarlet fever toxin in preventive immunization J A M A 82 544 1924) and produced severe local reactions fever nausea and in some cases a rash[5] and found that the previously positive skin test had been reversed They thought they had produced an active immunization but did not realize at the time that the immunity was primarily to the skin toxin and did not prevent subsequent "scarlet fever without rash"

The Dicks next communications ("A scarlet fever antitoxin" J A M A 82 1246 1924) dealt with the production of an antitoxic serum by immunizing a horse not with streptococci as in previous work (Refs 8 9 19) but with the

[3] All this had been noted by Berge in 1893 (Ref 7)

[4] Dochez's serum was produced by instilling scarlatinal streptococci into a mass of agar previously injected subcutaneously into the horse It was hoped that toxins absorbed from such a focus would produce antitoxic as well as antibacterial effects"

[5] This had all been shown years before by Gabritchewsky (Ref 7)

24 TRASK James D Jr and BLAKE Francis G Observations on the presence of a toxic substance in the blood and urine of patients with scarlet fever J Exper Med 40 381 1924

Although the possibility that a soluble toxin elaborated in the throat is responsible for the rash and perhaps other symptoms was suggested long before (Ref 7) it was not until the work of the Dicks (Ref 20) that the evidence became convincing Trask and Blake went a step further and actually demonstrated the presence of toxin in the blood They found that sera drawn early in the disease from scarlet fever patients produced large areas of erythema in susceptibles " whose own serum contained no rash blanching substance The toxic substance was neutralized by serum which gave a blanching test but not by negative sera The toxin was also neutralized by Dochez s immune horse serum (Ref 19) but not by normal horse serum

Trask and Blake still regarded the streptococci of scarlet fever as a specific group and they believed that all the generalized manifestations of the diseas were due to the soluble toxin " These concepts were later shown to be open to question

25 STEVENS Franklin A and DOCHEZ A R The occurrence of throat infection with Streptococcus scarlatinae without a rash J A M A 86 1110 1926 The epidemiology of scarlatinal throat infections sine exanthemate *ibid* 87 2137 1926

There were already many clinical observations of contacts with scarlet fever patients who developed sore throat without rash (Refs 2 7) It remained for Stevens and Dochez to isolate strains of streptococci from the throats of such patients and to prove by agglutination and absorption tests that they were identical in subjects with and without rash They also showed that in the type of infection without rash the Dick test was negative although the strain could be demonstrated to produce toxin which in turn was neutralized by antitoxin Throat infections without rash were found to occur in people who had previously had scarlet fever although the organism was a "Streptococcus scarlatinae" and produced toxin

Stevens and Dochez concluded that scarlatinal antitoxin was an efficient therapeutic agent in scarlatinal throat infections without rash a position which is not strongly supported with the type of scarlet fever seen today They were uncertain whether the absence of rash was always due to immunity to rash toxin or to failure of the streptococcus to produce the toxin and in general they raised the question of which components of the disease were the result of the local throat infection and which were caused by soluble poisons including the rash toxin

26 TRASK James D Studies in scarlet fever I The amount of scarlatinal toxin in the blood of patients with scarlet fever J Clin Investigation 3 391 1926

In an important series of papers from Blake s laboratory the studies which demonstrated the presence of erythrogenic toxin in the blood (Ref 24) were extended Trask worked out a system of measuring the amount of toxin in the blood of patients in terms of Dick skin test units (Ref 20) In different patients

to one of them and not to others Kirkbride and Wheeler later elaborated these studies ("Studies of the toxins of the hemolytic streptococci associated with scarlet fever" J Immunol **11** 477 1926 **13** 19 1927) W H Park and R G Spiegel ("Complexity of the scarlet fever toxin and antitoxin" J Immunol **10** 829 1925) also concluded that a variety of rash producing toxins might be formed by different strains of streptococci although in most cases toxin production seemed to be similar J D Trask Jr and F G Blake still later ("Heterologous scarlet fever J A M A **101** 753 1933) offered further evidence of heterogeneity among the toxins found in the blood in scarlet fever as well as among the scarlatinal antitoxins naturally found in man and they concluded that "polyvalency is desirable in therapeutic scarlatinal antitoxin These observations may explain the discordant results obtained with the early scarlatinal antisera (Refs 8 9)

The important paper of H Aranow and W B Wood Jr ("Staphylococcic infection simulating scarlet fever" J A M A **119** 1491 1942) should also be noted in this connection From a case of staphylococcic osteomyelitis with typical scarlatiniform rash no hemolytic streptococci could be grown but the hemolytic staphylococcus which was isolated from the lesion and from the blood produced an erythrogenic toxin which was neutralized by commercial scarlatinal antitoxin

22 ZINGHER Abraham The Dick test in normal persons and in acute and convalescent cases of scarlet fever J A M A **83** 432 1924

The widest application of the work of the Dicks (Ref 20) is the use of toxin" as a skin test for susceptibility to scarlet fever—the Dick reaction The contemporary position is comprehensively and authoritatively stated in this paper

23 BLAKE Francis G TRASK James D Jr and LYNCH John F Observations on the treatment of scarlet fever with scarlatinal antistreptococcic serum J A M A **82** 712 1924

Blake and his associates report clinical results with Dochez s antiscarlatinal horse serum (Ref 19) They laid stress on its value in diagnosis and described its capacity locally to blanch the rash in scarlet fever patients Also the serum would appear to possess very marked curative properties In some toxic cases there was complete recovery within 24–36 hours Forty to 60 cc of serum was usually adequate Blake was doubtful whether the serum would be effective in septic complications K Birkhaug (Studies in scarlet fever" Bull Johns Hopkins Hosp **36** 134 1925) also reported favorable results with Dochez s serum Forty cc administered during the first 3 days caused a prompt disappearance of the toxemia a critical fall in temperature and pulse rate and prompt fading of the rash The incidence of septic complications was low in cases treated prior to the fourth day

One is not convinced that these results are materially different from those obtained years earlier by Moser (Ref 9) Although scarlet fever is usually treated nowadays by penicillin (Ref 32) immune sera containing antibodies against the rash toxin and other possible soluble toxins would still seem indicated in very severe cases with intense initial toxemia

glutination so commonly encountered among streptococci (b) the nonspecific cross agglutination difficult of interpretation and (c) the existence of so many specific types as to make identification of strains impractical by type specific agglutination " In this extremely important paper she showed that immune sera satisfactory for precipitin tests with extracts of streptococci could be readily prepared By this method practically all hemolytic streptococci fell into five groups "which bear a definite relationship to the sources of the cultures " Most pathogenic strains from human disease including scarlet fever fall into group A which can be further subdivided by appropriate methods (Ref 29) This work made possible the final conclusion that the only feature which scarlatinal streptococci necessarily have in common is the ability to produce erythrogenic toxin and that such toxin may be produced by serologically distinct types

29 GRIFFITH F The serological classification of Streptococcus pyogenes J Hyg 34 542 1934

Griffith had already developed his method of rapid slide agglutination ("Types of haemolytic streptococci in relation to scarlet fever " J Hyg 25 385 1926) but in this paper he showed that the group A strains of Lancefield (Ref 28) could be subdivided into a large number of serological types Twenty seven types are described Many of these were isolated from cases of scarlet fever so that this work finally put an end to the idea of a specific race of scarlatinal streptococci

L A Rantz ("The serological typing of hemolytic streptococci of the Lance field Group A " J Clin Investigation 21 217 1942) gives a definitive sum mary of the Griffith types of hemolytic streptococci reported in various out breaks of scarlet fever in different localities It is pointed out that in any one season the types responsible are relatively few but that the same types do not predominate every season

30 STOCK Aaron A Studies on the hemolytic streptococcus I Isolation and concentration of erythrogenic toxin of the N Y 5 strain of hemolytic streptococcus J Immunol 36 489 1939

Attempts to concentrate and purify the rash toxin were obviously desirable In this work Stock prepared material of which 0 0001 μg was equivalent to one skin test dose (Dick) Later Stock ("IV Further purification and concentration of scarlet fever toxin " J Biol Chem 142 777 1942) prepared material which contained 200 000 000 skin test doses per milligram and he also found (L E Krejci A H Stock E B Sanigar and E O Kraemer "V The electrophoretic isolation of the erythrogenic toxin of scarlet fever and the determina tion of its chemical and physical properties " J Biol Chem 142 785 1942) by electrophoretic analysis that the material contained five distinct constituents and was a protein

31 BLOOMFIELD Arthur L and RANTZ Lowell A An outbreak of streptococcic septic sore throat in an army camp J A M A 121 315 1943

An important question is whether the soluble toxins of scarlatinal streptococci produce any clinical effects besides the rash The writers studied a mass infec-

toxin varied from 0 25 to 300 units but these values bore no relation to the general severity of the disease Blake and Trask amplified these observations (Studies in scarlet fever II The relation of the specific toxemia of scarlet fever to the course of the disease" J Clin Investigation 3 397 1926) and now showed that the presence of toxin ran parallel to the occurrence of the rash but did not follow all the manifestations of the disease especially the (late) septic features "The results suggest that the duration of the specific toxemia is measured by the duration of the rash which fades as the patient develops his own antitoxin or as therapeutic antitoxin is given E E Nicholls continued these studies ("III Infections with Streptococcus scarlatinae in persons with scarlatinal antitoxic immunity J Clin Investigation 3 411 1926) and showed that the old observation of scarlet fever without rash was to be explained by the subject s possessing specific antitoxic immunity even though the streptococci isolated from the throat produced toxin Nicholls final conclusion was important "Immunity to the toxin of Streptococcus scarlatinae as determined by the Dick test does not necessarily provide the immunity to *local pyogenic infections with Streptococcus scarlatinae*

27 GUNN William and GRIFFITH Fred Bacteriological and clinical study of one hundred cases of scarlet fever J Hyg 28 250 1929

The writers isolated and classified by the Griffith method of typing (Ref 29) the streptococci present in the throats of cases of scarlet fever Examinations were repeated at weekly intervals and in half the cases the same type of streptococcus remained In the others there was a change of type one or more times this was considered to be a reinfection V D Allison and W A Brown ("Reinfection as a cause of complications in scarlet fever wards" J Hyg 37 153 1937) confirmed and amplified these studies and H L de Waal (The serological types of haemolytic streptococci in relation to the epidemiology of scarlet fever and its complications J Hyg 40 172 1940) undertook the incredibly difficult task of making repeated cultures during the course of hundreds of cases of scarlet fever The most important of his interesting observations was that when a complication occurred it was associated with a streptococcus of a different type from that which was present on entry in 61 5 per cent of the cases

All this suggests that the streptococcus which is the primary cause of scarlet fever is at the time not behaving exactly like a non specific pyogen An analogy is the behavior of the pneumococcus in acute lobar pneumonia the pneumococcus produces a specific disease but may on occasion behave as a non specific pyogen causing suppuration in joints meninges or elsewhere The typhoid bacillus which primarily causes a specific non pyogenic disease—typhoid fever —may also alter its activity so as to produce an abscess

28 LANCEFIELD Rebecca C A serological differentiation of human and other groups of hemolytic streptococci J Exper Med 57 571 1933

Although Dochez and others (Ref 16) had concluded on the basis of agglutination reactions that the streptococci of scarlet fever fell into a single specific immunological group considerable evidence against this view soon accumulated Lancefield herself one of Dochez s original associates later criticized the agglutination reaction "on account of (a) the troublesome spontaneous ag

Section 8

ERYSIPELAS

Clinical	Refs 1 2 5
Epidemiology	Ref 1
General	Refs 1 2 5
Pathogenesis	Refs 3 6
Penicillin in	Ref 9
Serological reactions in	Ref 7
Serum therapy	Ref 4
Streptococcus in	Refs 3 6
Sulfonamides in	Ref 8
Therapy	Refs 2 8 9

tion of young men in an army camp presumably resulting from contaminated milk or food Several hundred men were taken sick almost simultaneously with an acute streptococcic sore throat It was shown that one strain--Type 15--was responsible Approximately one fourth of the patients had a typical scarlatinal rash in most cases no rash was seen As far as one could tell by clinical observation there was no over all difference in the severity course or complications in the two groups This would suggest that in this outbreak at least the effect of the toxin" was confined to production of the rash It is hard to *escape the conviction however that the hyperacute variety of scarlet fever* with death from toxemia" in the first few days must be due to other or more potent soluble toxins This view is supported by the undoubted beneficial effects of antitoxic sera observed in such cases in the past (Refs 9 22)

The whole question of the interpretation of scarlet fever without rash is analyzed in this paper

32 HIRSH *Harold* L ROTMAN KAVKA *Georgine* DOWLING *Harry* F and SWEET *Lewis* K *Penicillin therapy of scarlet fever--comparison* with antitoxic and symptomatic therapy J A M A 133 657 1947

The discovery of penicillin revolutionized the treatment of scarlet fever The writers clearly define the different effects of penicillin and of scarlatinal antitoxin in a large series of cases Penicillin resulted in fall in temperature lessening of sore throat lessened "toxicity" and marked lowering of incidence of pyogenic complications its effect was essentially antibacterial and reduced the number of carriers Antitoxin caused more rapid decline of temperature than did penicillin

An important point previously emphasized by W W *Spink and his associates* ("Sulfadiazine and penicillin for hemolytic streptococcus infection of the upper respiratory tract Arch Int Med 77 260 1946) is that unless one continues penicillin in adequate dosage for a fairly long period--7 to 10 days--relapse is likely to occur and the carrier state is likely to persist M Meads and his associates had also found ("Penicillin treatment of scarlet fever" J A M A 129 785 1945) in a small but carefully studied series that with even as little as 10 000 units of penicillin every 3 hours hemolytic streptococci disappeared from the throat cultures within 48 hours and if treatment was continued for 7 days the original types did not reappear Finally L Weinstein and L F Potsubay ("A comparison of symptomatic treatment gamma globulin and penicillin in the treatment of scarlet fever" J Pediat 37 291 1950) reviewed the growing literature on modern therapy and reported the results of treatment in 255 patients with "proved" scarlet fever Gamma globulin (presumably antitoxic) blanched the rash but had no effect on the streptococci in the pharynx did not seem to prevent carrier state and had little if any effect in preventing complications Penicillin on the other hand caused rapid disappearance of streptococci from the local focus terminated the carrier state and decreased the incidence of suppurative complications

From all this one may conclude that penicillin is adequate in the general run of scarlet fever patients and is the method of choice but in hyperacute "toxic cases antitoxin should be given *in addition*

However penicillin has completely altered the outlook on scarlet fever which is no longer to be dreaded as it was fifty years ago

Section 8

ERYSIPELAS

Clinical	Refs 1 2 5
Epidemiology	Ref 1
General	Refs 1 2 5
Pathogenesis	Refs 3 6
Penicillin in	Ref 9
Serological reactions in	Ref 7
Serum therapy	Ref 4
Streptococcus in	Refs 3 6
Sulfonamides in	Ref 8
Therapy	Refs 2 8 9

Section 8

ERYSIPELAS

THE early literature on erysipelas is confused and difficult first because many of the papers are inaccessible and second because erysipelas so often occurred in association with other clinical forms of streptococcal infection such as sore throat pyogenic abscess and puerperal fever The best general treatise still remains that of Lenhartz (Ref 5) although the long article by *A Vautrin P Spillman and L Ganzinotti* (*"Erysipele in Dictionnaire encyclopédique des sciences médicales* 1st Ser 35 [Paris G Masson (1887?)] 461) contains much interesting material

The bibliography of erysipelas should be considered in connection with that of scarlet fever (see pp 108 ff)

1 M DOWEL Ephraim Observations on erysipelas Dublin J M Sc 6 161 1835

In reading the early literature on erysipelas one is struck by the powerful epidemic tendency which was so often in evidence M Dowel s observations are a good illustration As far back as November more than the usual number of cases of erysipelas were observed but within the last three months it appeared to have assumed an epidemic character every kind of injury almost was followed by it it occurred after bleeding and leeching after burns simple as well as compound fractures venereal ulcers on the genitals and in the throat after the application of blisters sinapisms irritating ointments or liniments it occurred so constantly after operations that unless when absolutely necessary they were postponed frequently as long as was compatible with the safety of the patient" In addition to the epidemic character one is struck by the great number of cases in which a violent sore throat with swelling of regional lymph nodes preceded or followed facial erysipelas In all forms abscesses or suppurative complications were frequent One cannot help wondering whether there were active at the time strains of streptococci which had a special tendency to produce erysipelas At any rate the violent epidemic character and the association with outbreaks of puerperal fever are noted again and again A Hirsch (*Handbuch der historisch geographischen Pathologie* [2d ed Stuttgart Ferdinand Enke 1883] 2 270) gives a comprehensive review of such epidemics up to 1880 The subject is also discussed by Lenhartz (Ref 5 p 3)

2 TROUSSEAU A Clinique médicale de l Hôtel Dieu de Paris On erysipelas and especially erysipelas of the face 1 296 Paris J B Baillière et fils 1861

In this article Trousseau did not give a systematic description of erysipelas but he raised innumerable important questions In spite of the fact that he could not of course understand the dual role of the streptococcus which at one moment produces the characteristic superficial lymphangitis of facial erysipelas and in the next acts as an ordinary pus producer he sensed the answers to many vexing questions

He wondered what made erysipelas at times violent and epidemic following the least surgical interference whereas at other times in the same surgical ward years might elapse without a case He noted the association of epidemics of puerperal fever and of erysipelas He considered erysipelas definitely con tagious although there were exciting causes He distinguished surgical ery sipelas and medical erysipelas The latter although apparently idiopathic he believed could originally be traced to a small lesion on the lip in the nose etc thus bringing the two varieties in a sense together He noted the frequent appearance of fever and malaise for a day or two before the erysipelatous erup tion appeared He stressed the benign course and low mortality of "medical facial erysipelas in contrast to erysipelas arising in the course of another acute disease such as smallpox or in a patient reduced by tuberculosis He described erysipèle ambulant " the variety which slowly wended its way over the whole body or jumped here and there He described in graphic style epidemics of erysipelas or instances in which a number of people in a household successively contracted the disease such outbreaks are much less often seen today and give credence to the activity of special strains of erysipelas streptococci

Trousseau s treatment was far ahead of the times "Expectancy is then my treatment of facial erysipelas But gentlemen I feed them I feed them even if there is fever or delirium Thus instead of depleting the patients by loss of blood or the application of leeches behind the ears in place of giving emetics or repeated purgatives in place of keeping them on a restricted diet I remain a spectator of the struggle in which I know nature will emerge victorious if I do not disturb her operations To know how to wait is a great science in our art prudent waiting often explains successes it explains above all those ob tained sometimes by those of the Hahnemann sect "

3 FEHLEISEN [F] Ueber Erysipel Deutsche Ztschr f Chir **16** 391 1882

According to Fehleisen the first claim that erysipelas was due to a living organ ism was made by Hueter ("Verhandlungen arztlicher Gesellschaften " Berl klin Wchnschr **6** 358 1869) but an inspection of the article yields nothing worthy of mention Wladimir Lukomsky (Untersuchungen uber Erysipel " Virchows Arch f path Anat **60** 418 1874) described in fatal cases of erysipelas among other findings lymph vessels filled with micrococci Th Billroth and F Ehr lich (Untersuchungen uber Coccobacteria septica Arch f klin Chir **20** 403 1877) observed cocci in a mélange of septic infections some of which were associated with erysipelas The important fact however was that the idea of infection as a cause of erysipelas was in the air and the way was paved for the work of Fehleisen He first reported one fatal case (Untersuchungen uber Erysipel Sitzungsb d phys med Gesellsch Wurzburg 1881 p 126) in which he clearly saw micrococci in the superficial lymphatics but in the present definitive paper he described the process more in detail He saw and pictured beautifully the lymph channels of the epidermal and subepidermal layers of the skin choked with masses of cocci He concluded "Erysipelas is to be distin guished from the various forms of acute phlegmon not only by the clinical picture but by the peculiar micrococcus which differs from all hitherto de scribed pathogenic bacteria and seems to be a special species " Thus Feh

leisen anticipated later claims (Ref 6) of a special erysipelas streptococcus which in the end turned out to be incorrect (Ref 6) Soon thereafter Fehleisen summarized his work on erysipelas in a little book (*Die Aetiologie des Erysipel* [Berlin Theodor Fischer 1883]) In almost all of a series of rabbits and to a lesser extent in humans in whom cultures of erysipelas cocci were injected erysipelas was produced He also described the regression of superficial malig nant tumors following the artificial production of erysipelas in their vicinity He felt that erysipelas was definitely contagious and was spread from person to person by direct contact or by the mediation of instruments etc

Fehleisen isolated streptococci from erysipelas in pure culture as we said above he felt that this organism was specific for erysipelas and differed from the ordinary *Streptococcus pyogenes* both morphologically and biologically

Fehleisen s work on streptococci in the lymphatics in erysipelas was promptly confirmed by R Koch ("Zur Untersuchung von pathogenen Organismen " Mitt a d k Gsndhtsamte I 38 1881) using a similar method of biopsy Koch does not allude to Fehleisen by name and perhaps worked independently of him It is a question who really deserves priority

4 CHANTEMESSE Die Serumtherapie des Erysipels Munchen med Wchnschr 43 43 1896 [1]

Shortly after A Marmorek (Le Streptocoque et le serum antistreptococcique " Ann Inst Pasteur 9 593 1895) produced his antistreptococcal serum Chan temesse reported the effects of it in erysipelas He thought the results better than with other methods of therapy Of 501 treated cases the mortality was only 2 59 per cent The general condition was said to be improved but the spread of the eruption was not stopped in its tracks The treatment had a vogue for many years always with conflicting and questionable results Aside from the early work W S McCann (The serum therapy of erysipelas J A M A 91 78 1928) in a critical study questioned the value of serum therapy al though D Symmers and K M Lewis ("The antitoxin treatment of erysipelas " J A M A 99 1082 1932) felt that treatment with antitoxin" often shortened the disease and reduced the mortality However serum therapy has become a dead letter in the treatment of erysipelas since the advent of penicillin

5 LENHARTZ Hermann Erysipelas (Rose Rothlauf) und Erysipeloid Vienna Alfred Holder 1899

Lenhartz monograph definitive to date with bibliography takes up every phase of the subject bacteriological clinical epidemiological

6 FRANCIS Thomas Jr Studies on pathogenesis and recovery in ery sipelas J Clin Investigation 6 221 1928

Following Fehleisen s pioneer work there was a great debate as to whether there was a specific erysipelas streptococcus or whether any pyogenic strepto coccus could on occasion produce erysipelas The early observations dealing with this question pro and con are summarized in Lenhartz (Ref 5 p 17) J Petruschky ("Entscheidungversuche zur Frage der Specificitat des Erysipel Streptococcus " Ztschr f Hyg u Infectionskr 23 142 1896) pointed out that

[1] We have been unable to trace the original French paper

the alleged cultural and morphological differences between erysipelas and other streptococci described by Fehleisen did not hold He also emphasized the common clinical experience of one form of streptococcal infection passing over into another such as an infant who developed erysipelas by nursing a mother with a streptococcal mastitis Petruschky inoculated women who had cancer with strains of streptococci from non-erysipelatous sources and with these produced erysipelas He pointed out that the sort of disease to be caused by a given streptococcus depended rather on site of infection virulence of organism resistance of the infected person and the influence of already existing diseases

Certain it is that one cannot determine the specificity of a streptococcus from the disease picture The designations Streptococcus erysipelatis and Streptococcus pyogenes cannot be maintained as originally claimed R Koch and J Petruschky ("Beobachtungen uber Erysipel Impfungen am Menschen" Ztschr f Hyg u Infektionskr 23:477 1896) soon confirmed and amplified these observations and Petruschky ("Untersuchungen uber Infection mit pyogenen Kokken" Ztschr f Hyg u Infektionskr 18 413 1894) had already furnished impressive clinical examples of the non specificity of pyogenic cocci He summarized "There are pure streptococcol infections in which erysipelas develops in direct connection with a primary suppurative process contrariwise there are suppurative processes which begin in connection with a primary erysipelas and are caused by the same streptococcus Marmorek too—the pioneer in streptococcal serum therapy—concluded that strains from human disease were all of one sort A L Bloomfield ("The association of susceptibility to scarlet fever and acute tonsillitis" California & West Med 28 477 1928) reported the case of a young woman who had in immediate succession streptococcal otitis media acute tonsillitis infection of right maxillary antrum scarlet fever erysipelas and thrombophlebitis all presumably caused by the same strain of streptococcus

In spite of these facts K E Birkhaug (Studies on the biology of the Streptococcus erysipelatis I Agglutination and agglutinin absorption with the Streptococcus erysipelatis" Bull Johns Hopkins Hosp 36 248 1925) concluded that erysipelas was produced by a group of immunologically specific strains of streptococcus "These experiments indicate that it is possible to differentiate by immunological methods a group of hemolytic streptococci causing erysipelas from the group of hemolytic stretococci responsible for scarlet fever on the one hand and on the other from the large series of miscellaneous hemolytic streptococci producing a variety of pyogenic infections" F A Stevens and A R Dochez ("Antigenic relationship between strains of streptococci from scarlet fever and erysipelas" J Exper Med 43 379 1926) sustained the same thesis although it was soon questioned and finally disposed of by F Griffith ("The serological classification of Streptococcus pyogenes J Hyg 34 542 1934)

Meanwhile Francis discussed the whole question of the pathogenesis and recovery in erysipelas and demolished the claims of Birkhaug (IV Toxin production of the Streptococcus erysipelatis Proc Soc Exper Biol & Med 23 201 1925 "Erysipelas V Observations on the etiology and treatment of erysipelas with antistreptococcus serum J A M A 86 1411 1926) that recovery from erysipelas was associated with the neutralization of a soluble circulating toxin analogous to the rash toxin of scarlet fever

7 SPINK W W and KEEFER C S Studies of hemolytic streptococcal infection II The serological reactions of the blood during erysipelas J Clin Investigation 15 21 1936

Spink and Keefer analyzed the mechanism of recovery from erysipelas in the light of the development of antibodies They found that the antistreptolysin of the blood serum increased during the disease and that the streptococcidal power of the blood might also increase Some patients nonetheless developed erysipelas in the face of titers of these substances as high as in controls The writers bring out clearly the complexity of the situation

8 SNODGRASS W R and ANDERSON T Sulphanilamide in the treatment of erysipelas Brit M J 2 1056 1937

Snodgrass and Anderson had reported favorable results in the treatment of erysipelas with prontosil (Prontosil in the treatment of erysipelas" Brit M J 2 101 1937) They now reported similar success with sulfanilamide and a little later Snodgrass Anderson and Rennie (Sulphamido chrysoidine sulphanilamide and benzyl sulphanilamide in the treatment of erysipelas" Brit M J 2 399 1938) reported a mortality of only 2 06 per cent in 242 cases treated with sulphanilamide and related drugs

9 MORTENSEN Ole The efficacy of penicillin and 2 sulfanilamido-5 methyl 1 3 4 thiodiazole ("Lucosil) in the treatment of erysipelas Acta med scandinav 139 465 1951

Although there are earlier reports of treatment with penicillin of single cases of erysipelas such as that of A L Bloomfield W M M Kirby and C D Armstrong ("A study of penicillin failures J A M A 126 685 1944) we have been unable to find an account of a large series until the present paper Ninety eight patients were treated with penicillin and fifty two with "Lucosil" Although the difference in results with the sulfonamides and penicillin were slight penicillin seemed to produce a more rapid fall of temperature and subsidence of cutaneous symptoms It is now (1956) regarded as the treatment of choice

Section 9

RHEUMATIC FEVER

Topic	References
Antibodies in rheumatic fever	Ref 24
Bacteriology	Refs 17 22 23 28
Chorea	Ref 6
Clinical	Refs 2 3 5 7 8 14
Diagnosis	Ref 14
Epidemiology of rheumatic fever	Ref 15
Etiology	Refs 17 22 28
Fibroid nodules	Refs 4 9
General	Refs 2 3 5 7 8 13 14 20 22
Heart in rheumatic fever	Ref 18
Heredity in rheumatic fever	Ref 11
Laboratory tests for rheumatic fever	Ref 24
Pathology	Refs 16 19 26 30
Postcommissurotomy syndrome	Ref 31
Prophylaxis of rheumatic fever	Refs 25 27

(Continued on following page)

Pulmonary lesions	Ref 21
Rheumatic fever and heart disease	Refs 1 3 4 5
Salicylate therapy	Ref 10
Sore throat and rheumatic fever	Refs 7 12
Steroid hormones in rheumatic fever	Ref 29
Treatment	Refs 5 7 8 10 29

Section 9

RHEUMATIC FEVER

SO MUCH has been written on every phase of rheumatic fever that the bibliographer is confronted with an almost hopeless task We call the reader s attention again to the fact that the present list is compiled not for spe cialists but for general doctors and medical students although it is certainly incomplete we have tried to mention every reference which deals with a really fundamental advance in knowledge of the subject

Excellent older accounts of acute rheumatic fever are those of Senator ("Poly arthritis rheumatica acuta " in H von Ziemssen *Handbuch der speciellen Pa thologie und Therapie* [Leipzig F C W Vogel 1875] 13 12) and of A Pribram (*Der acute Gelenkrheumatismus* [Vienna Alfred Holder 1901]) The latter monograph of some five hundred pages is especially comprehensive it leaves no phase of the disease to date untouched and it concludes with a bibli ography of nearly two thousand titles Among the numerous briefer English books should be mentioned especially that of Cheadle (Ref 14) The mono graphs on the relation of streptococci to rheumatic fever (Ann Pickett Thom son Res Lab [London Baillière Tindall & Cox 1928] Vol 4 Part 1) contain useful bibliographies The books by Coburn (Ref 22) and by Wilson (Ref 11) deal with certain special phases of the subject but are of general interest and have good bibliographies Finally there is assembled in a symposium on *Rheu matic Fever* edited by L Thomas (Minneapolis University of Minnesota Press 1952) a series of recent articles which really cover the whole subject An excellent brief summary of the disease is given by L. A Rantz (Ref 24)

Invaluable critical bibliographies of recent literature on rheumatic fever are included in the "rheumatism reviews which have appeared under the leader ship of P S Hench in Ann Int Med 9 883 1936 10 754 1936 11 1089 1938 12 1005 1939 13 1655 1940 14 1383 1941 15 1002 1941 28 66 1948 39 498 1953 To these should be added the article by C B Perry (Re view of the literature on acute rheumatism during the years 1939–1945 " Ann Rheumat Dis 6 162 1947)

1 BAILLIE M The morbid anatomy of some of the most important parts of the human body p 46 2d ed London J Johnson 1797

Baillie gives a good description of mitral disease "The valvular apparatus be tween the auricles and ventricles is also occasionally thickened having lost all its transparency and having an opaque white color The chordae tendineae like wise become thicker than natural " (p 32) And as to symptoms he says "When the heart is much enlarged it is attended with palpitations but more commonly the pulse is feeble and irregular The causes which produce a marked growth of the heart are but little known one of them would seem to be *rheumatism attacking this organ* [italics ours] " In a footnote he adds "Dr Pitcairn has observed this in several cases "

Here then is one of the first hints of a relation between rheumatic fever and valvular heart disease For the most part however no one at the time suspected such a relation John Abernethy ("On a diminution [in consequence of disease]

of the area of the aperture by which the left auricle of the heart communicates with the ventricle of the same side Med Chir Tr 1 27 1815) for example describes accurately the clinical features and autopsy findings in two cases of mitral stenosis with no hint of "rheumatism preceding the heart disease

2 HAYGARTH J A clinical history of diseases Part first Being 1 A clinical history of the acute rheumatism London Cadell & Davies 1805

In this little monograph Haygarth gives an excellent clinical description of acute rheumatic fever The symptom peculiar to this disease is an inflammation of the joints which often increases to great violence with swelling soreness to touch and sometimes redness of the skin It attacks most if not all the joints of the body in different patients often two three or more joints at a time leaving some and going to others in succession frequently returning again to each of them several times during the disease [p 16] Exposure to cold or moisture is the chief cause of the acute rheumatism [p 17] This very formidable and extremely painful disease continues for many weeks more or less The remedies usually employed in the acute Rheumatism are bleeding by the lancet or leeches blisters antimony sudorifics saline medicines and the warm Bath The principal purpose of this publication is to recommend the Peruvian Bark in preference to all other remedies [p 18] For whatever it means we quote the following Hence we learn that persons who have been previously affected with the acute or chronical Rheumatism the gout or *sore throat* [italics ours] especially the first are most liable to suffer attacks of this disease" (p 30)

But throughout the book including numerous case reports there is not a word to indicate that the writer had any idea of an association with heart disease

3 DUNDAS D An account of a peculiar disease of the heart Med Chir Tr 1 37 1809

"There is a disease of the heart which I apprehend is not very uncommon no less than nine cases of it having in the course of thirty six years fallen under my care I have heard of several other cases and yet I do not believe any account of it is to be found in any medical author " Dundas then gives a good description of what is clearly mitral disease with auricular fibrillation But significant is the following paragraph In all of the cases which I have seen this disease has succeeded one or more attacks of rheumatic fever the inflammation pain and swelling of the extremities after having shifted from one joint to another for many weeks subsided but the affection of the heart continued producing in the progress of the disease and towards its close a considerable disposition to dropsy under which the patient lingered for ten months All those I have seen were young persons One I think cannot recover and one is apparently well having survived the attack four years He has had no rheumatic affection for two years and a half but the action of the heart is still very violent and easily increased by exercise His recovery is attributed to a very strict adherence for a long time to a vegetable and milk diet and great attention to avoid any considerable exertion At autopsy cardiac enlargement was always present and in one case "upon opening the left ventricle was found an irregular excrescence of the nature of polypus attached to

and nearly occupying the whole of one of the valvulae mitrales" Could this be an instance of bacterial endocarditis? Others were also aware of the relationship since Mr Pemberton described a patient who "had been in his youth and indeed even to the time he was taken ill (aged 36) subject to acute rheumatism" Then comes an exquisite description of what was probably the onset of auricular fibrillation "He was seized with a considerable pain at the heart and a difficulty of respiration great palpitation and great anxiety He conceived that the smallest motion of the body would have instantly destroyed him and this dread seemed to have totally bereft him of the power of utterance" So too Dr Marcet gave an account of "two cases of translation of rheumatism from the extremities to the chest "

Dundas concludes "The knowledge that this disease is always the consequence of or is connected with rheumatic affection points out the necessity of attending to the translation of rheumatism to the chest and shews the importance of employing very vigorous measures to remove it as soon as possible but wherever it has made any considerable progress I fear it will baffle every effort" words still as good today as 150 years ago At any rate it is clear that the relation of rheumatic fever to mitral disease was becoming common knowledge in the early nineteenth century

4 WELLS W C On rheumatism of the heart Tr Soc Improvement M & Chir Knowledge 3 373 1812

Wells tried to set the record straight to date He emphasized the unpublished observations of Dr David Pitcairn who "about the year 1788 began to remark that persons subject to rheumatism were attacked more frequently than others with symptoms of an organic disease of the heart He then alluded to Baillie s observations which are certainly brief and inadequate (Ref 1) He mentioned the work of Dr Odier[1] of Geneva and of Dr Dundas (Ref 3) and then reported cases of his own which were undoubtedly rheumatic valvular disease but not nearly so well described as those of Dundas Wells clearly described subcutaneous fibroid nodules in his Case II "Many of the tendons of the superficial muscles in this patient were studded with numerous small hard tumours an appearance I have observed only in one other person " (see also Ref 9)

5 BOUILLAUD J New researches on acute articular rheumatism in general Translated by James Kitchen Philadelphia Haswell Barrington & Haswell 1837

Bouillaud s ideas of rheumatic fever were as follows "Pain heat redness tumefaction with or without fluctuation of the affected joints—such are the local *symptoms of acute articular rheumatism The pain is increased by touching*

[1] Odier s book *Manuel de médicine practique etc par Louis Odier* (Geneva J J Paschaud Libraire 1803) is reviewed in detail in the Edinburgh M & Surg J 2 446 1806 The reviewer states "Among the various symptoms which are apt to supervene on acute rheumatism, and to degenerate afterwards into a chronic complaint Dr Odier mentions an affection of the heart Its characteristic symptoms are frequency and irregularity of the pulse oppression and cough It is frequently accompanied with anasarcous swellings "

[2] The original French edition *Nouvelles recherches sur le rhumatisme articulaire* (Paris 1836) was unfortunately not available to us

and by the slightest motion Fluctuation a sign of articular effusion can only be well discovered in the large joints and especially in the knees Violent fever accompanies above local symptoms Articular rheumatism considered by itself and apart from various complications shows itself with great variety both in extent and intensity Thus as to extent it sometimes is so slight as to be dissipated in twenty four hours then again so severe as to resist whole months unless the most energetic measures are used Whilst the acute rheumatism easily leaves one or more joints it generally does so to in vade others whatever may be the mechanism which presides over this displace ment By the acknowledgment of every observer the duration of this disease is very long the medium term being from 40 to fifty days [pp 31–34] The termination of acute articular rheumatism although often of some duration is rarely fatal But yet endocarditis pericarditis pleuritis with which it coin cides sometimes produces death [p 35]

It is clear then that Bouillaud had a much less complete view of rheumatic fever than we have today He thought that the disease consisted simply of acute inflammation of joints which often spread to the heart He believed that acute rheumatism was in the group of phlegmasias or acute inflammations "Can any one indeed refuse the title of phlegmasia to a disease which at its height is characterized in reference to its local symptoms by pain heat swelling and redness and with respect to its general state by a most violent fever [p 43] As to the determining causes they may be reduced on final analysis to one alone viz the impression of cold especially when humid [p 40] Bouillaud also thought that fatigue was a contributory cause The fact however that he and his contemporaries at times found frank pus in the joints of patients with "acute articular rheumatism" shows that they confused the disease with pyogenic arthritis possibly gonococcal which may well mimic rheumatic fever

Bouillaud was a curious mixture of the new clinicopathological school and of old Galenic ideas He recommended following Sydenham bleeding as an al most specific cure for rheumatic fever In Case III for example the procedure consisted of the following First day of treatment—bleeding to six bowls in the morning and four in the evening In the interval scarified cups over the pre cordial region to the extent of three bowls (in all 52 oz) Second day four bowls forty leeches Third day—four bowls Fourth day—three bowls Fifth day —most of the joints are free from swelling the pain and the fever have dis appeared Convalescent—soup "

Bouillaud was emphatic about the relation of rheumatic fever to heart dis ease "It is I will venture to say a discovery worthy of some attention to wit the almost constant coincidence either of endocarditis or of pericarditis or endo pericarditis with violent acute articular rheumatism This fact is of such vast importance that it constitutes in some measure a true revolution in the history of acute articular rheumatism" (Preface p iii) It was following Laennec s introduction of the stethoscope that diagnosis of valve lesions during life became possible in contrast to the anatomical diagnosis of the earlier ob servers (Refs 1 3 and 4) Bouillaud was a pioneer in physical examination of the heart (see e g his *Traite clinique des maladies du cœur* [Paris J B Baillière 1835]) In auscultating the sounds of the heart in some individuals still laboring under or convalescing from acute articular rheumatism I was not a little surprised to hear a strong file saw or bellows sound [*bruit de râpe de*

scie ou de soufflet] such as I had often met with in chronic or organic indura tion of the valves with contraction of the orifices of the heart [p 9] Pericarditis exists in about half the patients affected with acute articular rheumatism [p 12] Endocarditis like pericarditis manifests itself under the same influences as acute articular rheumatism [p 12] But in these phlegmasias there exist nice degrees and I acknowledge that in such cases the diagnosis is both diffi cult and uncertain [p 16]" He also clearly described cases of valve lesions persisting or becoming evident long after all signs of articular rheumatism had disappeared

Bouillaud was apparently unfamiliar with or at least gave no credit to the earlier observers (Refs 1 3 and 4) on the relation of rheumatism to heart dis ease

6 SÉE De la chorée rapports du rhumatisme et des maladies du cœur avec les affections nerveuses et convulsives Mém Acad méd Paris 15:373 1850

As early as 1821 the association of chorea with rheumatic fever was clearly recognized James Copland (Case of chorea etc with an account of post mortem appearances" London M Repository 15:23 1821) for example stated that Pritchard the subject of the following case was attacked at the age of nine years with acute rheumatism Soon after his recovery chorea St Viti supervened" Later he had another violent bout of rheumatic fever with cardiac involvement and "he had become again seized by chorea similar in all its symptoms with the attack from which he had recovered fourteen months before

The patient died and at autopsy the cord which itself appeared normal was surrounded with coagulable lymph and turbid serum The interpretation of these findings is difficult J Roeser ("Carditis unter der Form von Chorea St Viti" J d pract Heilk 67:54 1828) reports a child suffering from typical chorea who at death showed pericarditis and inflammation of the heart Richard Bright (Cases of spasmodic disease accompanying affections of the pericardi um" Med Chir Tr 22 1 1839) describes the case of a young man whose trouble began with "general rheumatic symptoms pains in the limbs with puffi ness and swelling of the wrists and some other joints When all this was sub siding "I found him labouring under the most fully marked symptoms of severe chorea His head was constantly thrown from one side of the bed to the other His lips were closed and opened with a smacking sound and when he desired to put out his tongue it was protruded with all the forced grimace and difficulty observed in chorea There were signs of organic heart disease He died and at autopsy there was found acute pericarditis and endocarditis Dr Yonge of Plymouth (Case of cerebral disturbance dependent upon disease of the peri cardium Guys Hosp Rep 5 276 1840) reports a somewhat similar case He states that about a fortnight since he was confined to bed by rheumatic fever caused by exposure to night air and damp from falling asleep in a grave yard where he was watching a corpse He then developed chorea and at death was found to have acute endocarditis H M Hughes ("Digest of 100 cases of chorea" Guys Hosp Rep 4 2d ser 360 1846) presents a careful analysis of cases many of which were clearly associated with rheumatism and/or endo carditis

But these case reports are insignificant in comparison with the monumental monograph of Sée which occupies 150 quarto pages Among the characteristics of chorea "most constant and most essential are irregular and disordered movements almost always continuous and unmotivated which without absolutely impairing the action of the will on the affected muscles removes all synergism from their contractions all precision from their efforts " Every feature of the disease is taken up in detail too great for us to review but the section on association with rheumatism is of special importance In 128 cases of chorea See found that 61 coincided with articular inflammation or pain In the vast majority articular rheumatism preceded the chorea but there were also cases concomitant with or preceding the rheumatic fever The material is well documented by references to the literature There is a good deal of matter in this long essay which today seems irrelevant and incorrect, but the association of chorea with rheumatic fever is emphatically emphasized The essential anatomical lesions were "phlegmasias [inflammations] pseudo membranous or purulent of the serous membranes especially of the pericardium or the arachnoid The anatomical findings in the acute phase are a pseudo membranous inflammation a serous congestion or a simple hyperemia In the chronic stage one finds the products of plastic lymph organized in the manner of patches opacities thickenings adhesions fibrous indurations sometimes fibro cartilaginous or bony " One doubts whether all these cases were simple chorea J Godwin Greenfield and J M Wolfsohn ("The pathology of Sydenham s chorea Lancet 2 603 1922) give an excellent historical review and then report histological studies of a fatal case of chorea They describe thrombosis of vessels round cell infiltration and changes in nerve cells and conclude that chorea is "a meningo-encephalitis of rheumatic origin "

7 SUTTON H G Cases of rheumatic fever treated for the most part by mint water collected from the clinical books of Dr Gull with some remarks on the natural history of that disease Guy s Hosp Rep 11 3d ser 392 1865

In studying the treatment of acute disease it is impossible not to observe how confidently remedies various and even opposite in their modes of action have been recommended It is probably while endeavouring to explain the effects so little to be expected from such different kinds of treatment an opinion has been gradually formed that the natural course of the disease had more to do with the result than the remedy " Gull and Sutton therefore proceeded to study the natural course of the disease in patients treated only by rest and safeguarding They noted that all the symptoms might subside in 5 6 7 or 8 days unaided by treatment Every type of case is described brief long recurrent with and without cardiac involvement "It would appear that those cases in which the symptoms are acute tend to get well much sooner than those in which the symptoms are sub-acute "

Since mention of antecedent sore throat or respiratory infection so much stressed today is conspicuous by its absence in the early descriptions the following case in Sutton s report is of special interest and importance "A young lady was suffering from sore throat she was very subject to enlarged tonsils Some yellow cheesy looking substance was noted on the tonsils She appeared depressed, and was sweating freely but no acid odour She was kept in bed for

3 days then appearing much better she was allowed to get up One day about a month after she had had this throat affection she complained of pain in the right knee There was pain first in one knee then in the other also in the ankles but no swelling so she continued for eight or ten days" About the end of that time she became worse and "a harsh grating to and fro murmur was heard over the heart"

"In relation to the rheumatic state is the very important question when we have lost all the symptoms of rheumatic fever—has the patient lost the rheumatic condition of the system The case of Dr Rees would lead us to think not"

"A perusal of the above cases tends to show that the best treatment for rheumatic fever has still to be determined The cases show that too much importance has been attached to the use of medicines especially in those acute cases where the tendency to a natural cure is the greatest"

In a subsequent number ("A second report of cases of acute rheumatism" Guy s Hosp Rep 12 3d ser 509 1866) Sutton gives admirable descriptions of more cases of rheumatic fever both these papers are preliminary to the study of Gull and Sutton (Ref 8)

8 GULL, W W and SUTTON H G Remarks on the natural history of rheumatic fever Med Chir Tr 52 43 1869

In the first half of the century students of rheumatic fever devoted themselves largely to the trial of various remedies Many papers appeared in which claims were made for the virtue of one or another form of medication There was much special pleading and many post hoc fallacious conclusions We have already pointed out Bouillaud s emphasis on bleeding as the only useful remedy (Ref 5) D J Corrigan on the other hand ("Observations on the treatment of acute rheumatism by opium" Dublin J M Sc 16 256 1840) strongly advocated the use of opium "The most important rule to be remembered is that *full and sufficient* doses shall be exhibited" He prescribed it in increasing amounts until a beneficial effect was obtained The first indication that the proper dose had been reached is "the statement of the patient who in reply to an inquiry as to how he has passed the night, probably says that he has not slept but that he is free from pain and feels comfortable" Kersten ("Beitrage zur Behandlung des hitzigen Gelenk Rheumatismus" Deutsche Klin 1 16 1849) also described a rigid dosage scheme for opium he was not so certain as Corrigan however that this treatment prevented cardiac complications J J Furnivall ("On the pathology of acute rheumatism and on the prevention of heart disease" Lancet 1 304 1844) after commenting on the obscurity which enveloped the pathology of acute rheumatism concluded that alkali was the proper treatment because of the acid predominant in the system and "as a thinner of the fibrine superabounding in the blood" Innumerable other medicines and schemes of treatment had their advocates

Soon however critical papers began to appear Thomas K Chambers ("Statistics of the treatment of rheumatic fever" Brit M J 2 237 1863) found that patients treated with nitrate of potash remained in hospital for a mean stay of 40 days those treated with bicarbonate of potash q 2 h stayed 34 3 days those treated with "a less quantity of the same stayed 40 0 days and those treated without drugs stayed 30 0 days When patients were bedded in blankets in

stead of in sheets the occurrence of pericarditis and endocarditis was lower Obviously these figures do not speak strongly for the virtue of medicines

But Gull and Sutton approached the problem in a highly unbiased attitude In this paper we are desirous of bringing under the notice of the profession the particulars of a few more cases of rheumatic fever which have been treated by mint water or in other words by absolute rest and regulated diet unaided by medicine We are now desirous of pointing out what appears to be the natural course of rheumatic fever with reference to the heart to show in what proportion of cases the heart has become diseased when the patients were treated by mint water and to consider if there be any evidence to prove that the heart is more frequently involved where cases are treated by alkalies lemon juice or by the application of blisters to the joints They concluded emphatically that none of these methods of therapy influenced the course or duration of the disease or prevented cardiac complications "The reason why the heart did not become diseased when rheumatic fever was treated by alkalies or blisters to the joints is to be attributed not to the influence of drugs but to the natural course of the disease At present therefore as regards treatment our cases seem to show that we are limited to a careful regimen of the patients Rest mechanical and physiological rest in the very outset of the disease We ought not to wait until the rheumatic process has become well developed in the joints for it appears to us that the heart becomes involved simultaneously with the joints and by rest we hope to quiet the heart s action and so prevent it becoming diseased

Gull and Sutton s study is a model of critical approach and reasoning It gave a sound orientation to therapy and prepared the way for the introduction of salicylates in treatment of rheumatic fever (Ref 10)

9 MEYNET P Rhumatisme articulaire subaigu avec production de tumeurs multiples dans les tissus fibreux periarticulaires et sur le perioste d un grand nombre d os Lyon méd **20** 495 1875

Wells (Ref 4) appears to have been the first to mention fibroid nodules but his account is brief and inadequate In his textbook on *Diseases of Children* (Philadelphia Lindsay & Blakiston 1868) Thomas Hillier however referred to a child with "aggravated chorea who developed under his scalp "a number of hard round lumps about the size of peas and horse beans the skin moves over them but they are firmly attached to the bone They are neither red nor tender on pressure Later there appeared a swelling on the inner condyle of the femur Dr Jenner saw him with me and feared that these growths might be malignant but in favor of rheumatism is the circumstance that there is now a loud systolic murmur at the heart s apex The boy got well and the lumps disappeared

But Meynet seems to have been the first to direct special attention to sub cutaneous fibroid nodules He reported the case of a boy who had several rheumatic relapses *Along the course of each of these tendons one found a rosary of little lumps about the size of a lentil or of a pea hard to the touch not painful and intimately adherent to these tendons all around these joints one finds little tumors Furthermore a point of importance to note these nodosities appear and disappear with great speed we have seen them so to speak spring up under our eyes from day to day and we have likewise seen*

them disappear Which is the native and precise seat of these neoplasms? It is evident to us that they are due to rheumatism In our young subject it is evident that it is above all the fibrous tissues which are involved—joints periosteum and tendons" Meynet left little to be described further as regards the clinical features E Troisier and L Brocq ("Les Nodosités sous cutanées éphémères et le rhumatisme" Rev méd Paris 1:297 1881) reported another case and gave a thorough discussion of the subject At about the same time there appeared the report of H Hirschsprung ("Eine eigenthumliche Localisation des Rheumatismus acutus im Kindesalter" Jahrb f Kinderh 16:324 1881) in which he gave detailed reports of several cases He concluded "The nodules must be considered as new growths of connective tissue of a chronic inflammatory sort with a tendency to necrobiosis They are probably derived from tendons the tissues of which they resemble"

To T Barlow and F Warner (On subcutaneous nodules connected with fibroid structures occurring in children the subjects of rheumatism and chorea" Tr Internat M Cong 14:116 1881) however goes the credit for the first detailed and comprehensive account They give an analysis of 27 cases and described the natural history of these nodules in great detail A nodule was removed during life and microscopic sections were made which showed "wavy strands of fibrous tissue with caudate spindle shaped nucleated cells and abundant vessels It had indeed many of the characters of organizing granulation tissue" B F Massell J R Mote and T D Jones ("The artificial induction of subcutaneous nodules in patients with rheumatic fever" J Clin Investigation 16:125 1937) found that "the injection of the patient s own blood into the subcutaneous tissues of subjects with rheumatic fever frequently results in the appearance of subcutaneous nodules in the area injected They are clinically indistinguishable from nodules occurring spontaneously

Every phase of the subcutaneous fibroid nodule is fully discussed in H Keil s definitive monograph ("The rheumatic subcutaneous nodules and simulating lesions" Medicine 17 261 1938) with over three hundred references

10 MACLAGAN T The treatment of acute rheumatism by salicin Lancet 1:342 1876

"The idea of treating acute rheumatism by salicin occurred to me in November 1874 I had at that time under my care a well marked case of the disease (Case 1) which was being treated by alkalies but was not improving I determined to give salicin but before doing so took myself first five then ten and then thirty grains without experiencing the least inconvenience or discomfort I gave to the patient referred to twelve grains every three hours The result exceeded my most sanguine expectations On the following day after 84 grains of salicin had been taken the pulse had gone down to 100 the temperature to 99 6 (from 102 8 the previous day) a fall of over 3 the pain and swelling of joints but especially the pain had much abated the joints could be moved a little and the patient expressed himself as being much better" Maclagan reported eight cases with graphic charts showing striking drops in temperature He concluded that salicin was a valuable remedy in acute rheumatic fever that the more acute the fever the more marked the benefit usually within 24–48 hours and that there was great relief of pain "I shall be greatly obliged if those who try the remedy and do not care to publish their observations

would kindly forward to me the results of their experience be it favourable or otherwise"

At about the same time Stricker ("Uber die Resultate der Behandlung der Polyarthritis rheumatica mit Salicylsaure" Berl klin Wchnschr 13 1 15 1876) no doubt independently treated patients with acute rheumatic fever in Traube's clinic with salicylic acid All the patients were freed of fever and local manifestations within 24–48 hours He emphasized that this effect was something apart from the general antipyretic action of the drug L Reiss ("Nachtrag zur innerlichen Anwendung der Salicylsaure insbesondere bei dem acuten Gelenkrheumatismus" Berl klin Wchnschr 13 86 1876) soon amplified Stricker's report Meanwhile Broadbent ("Treatment of rheumatic fever by salicylic acid" Lancet 1 530 1876) who was unaware of Maclagan's report but who knew of Stricker's work reported similar excellent results "Few diseases have had brought against them a heavier armament of drugs than has acute rheumatism It has been stormed by alkalies and salines attacked by acids assaulted by perchloride of iron and by quinine surprised by propylamine and ethylchlorure drained by venesection and purgatives flooded alternately with hot and cold water alarmed with blisters blasted with hot air lulled by opium and appeased by chloralhydrate In addition to these it has been constantly harassed by the raids of lesser foes such as lemon juice citric acid belladonna and iodide of potassium Salicylic acid has been shown by Stricker to be able to prevail against some cases of acute rheumatism and Dr Broadbent's experience seems to confirm this character In a letter to the Lancet (1 585 1876) Maclagan complained that Broadbent did not grant him due priority to which Broadbent replied with a gracious explanation (*ibid* p 619)

The use of salicylic acid or salicylate was promptly accepted as of real value J L Miller ("The specific action of salicylates in acute articular rheumatism" J A M A 63 1107 1914) studied the length of time that patients with acute rheumatic fever treated with and without salicylates remained in the hospital 1 907 patients with salicylates averaged a 32 28 days stay 1 600 without salicylates 33 6 days Miller concluded therefore that statistics show that patients receiving salicylate are free from pain much earlier than those not treated As the treated patients much more frequently relapse the period of stay in the hospital is the same P J Hanzlik ("Actions and uses of the salicylates and cinchophen in medicine" Medicine 5 197 1926) presented a monumental review of the whole subject superseded only by Martin Gross and Leon Greenberg's monograph *The Salicylates A Critical Bibliographical Review* (New Haven Hellhouse 1948) with bibliography of some four thousand titles

In 1943 A F Coburn ("Salicylate therapy in rheumatic fever a rational technique" Bull Johns Hopkins Hosp 73 345 1943) proposed the treatment of acute rheumatic fever by large doses of salicylates intravenously with control of blood levels He thought that this method was more effective in preventing cardiac involvement than standard oral administration The method was extensively taken up but G E Murphy (Bull Johns Hopkins Hosp 77 1 1945) in a careful study showed that in several patients given intravenous salicylates in large doses "characteristic rheumatic lesions developed in a variety of sites during the course of salicylate therapy" B V Jager and R Alway ("The treatment of acute rheumatic fever with large doses of sodium salicylate" Am J M

Sc 211:273 1946) were also unenthusiastic about Coburn s method and now (1956) it seems to have dropped into disuse

11 GOODHART J F On the rheumatic diathesis in childhood Guys Hosp Rep 25:3d ser 103 1880

The large number of reports in the modern literature on the occurrence of rheumatic fever in families makes one forget that this fact was recognized over seventy five years ago P H Pye Smith (Analysis of the cases of rheumatism and other diseases of the joints" Guys Hosp Rep 19:3d ser 311 1874) is quite emphatic "There can be no doubt that a tendency to rheumatic fever is inherited" He gives an analysis of 68 cases in which the patient asserted that one or more of his blood relatives had been attacked by rheumatic fever Goodhart goes into the matter much more thoroughly "Acute rheumatism in children is in the majority of cases inherited" His paper concludes with a table of cases indicating the occurrence of rheumatic manifestations in the family For example of children with acute rheumatic fever we have statements such as the following Girl aged 9 Father has had rheumatic fever Boy aged 9 Mother has had rheumatic fever Girl aged 4 Father died with rheumatic fever and heart disease etc A E Garrod and E H Cooke ("An attempt to determine the frequency of rheumatic family histories amongst non rheumatic patients" Lancet 2 110 1888) state "It is universally admitted that rheumatism is an extremely hereditary disease" Nonetheless the writers attempted to find out how often the relatives of non rheumatic patients gave a history of rheumatic disease The figure was about 20 per cent as against 30–35 per cent in the relatives of rheumatic patients

But Cheadle s discussion (Ref 14 "Occasional lectures on the practice of medicine" p 227) is most impressive "The second personal factor viz hereditary predisposition is one of the most potent The tendency to rheumatism is transmitted as strongly as the tendency to gout In thirty two consecutive cases out of my private notebooks in twenty three that is 70 per cent there was a definite history of rheumatic fever in near blood relations If chorea and erythema be taken as sufficient evidence of rheumatism the proportion is raised to 93 per cent. A case is recorded which shows remarkable family proclivity to the disease A rheumatic mother had twelve children and eleven of them had rheumatism before the age of twenty as might be inferred when the proclivity is inherited from both parents the tendency is greatly intensified not only is the liability to the disease increased but its severity and persistence are increased also Now it occurred to me that this extraordinary tendency of rheumatism to develop in certain families might be due to some special faults of locality or circumstances but careful inquiry into a number of cases showed me that they arose in various localities in members of the family when in different places and under different conditions"

During subsequent years many papers which added little were published on the same question The recent studies of M G Wilson and M D Schweitzer (Rheumatic fever as a familial disease environment communicability and heredity in their relation to the observed familial incidence of the disease" J Clin Investigation 16 555 1937) seem however to carry the subject further In a careful study of families under controlled conditions they found as had Cheadle that "there did not appear to be a direct relation between the

environments studied and the incidence of rheumatic fever There was no direct relation between the type and source of exposure and the resulting activity Intimate contact (familial exposure) and casual contact (extrafamilial exposure) were equally effective The hereditary mechanism involved was a single autosomal recessive gene Their general conclusion is that susceptible" persons acquire rheumatic fever much more readily than others but they do not determine from these studies the exact role of environment and contagion in the acquisition of the disease J R Paul and R Salinger (The spread of rheumatic fever through families J Clin Investigation 10 33 1931) had come to similar conclusions and thought that the spread of rheumatic fever through families strongly suggested infection with the role of environment and hereditary predisposition as yet undetermined It was of interest that rheumatic activity was often accompanied by evidence of respiratory tract infection An intensive analysis of the whole problem with full bibliography is given by Wilson in her book *Rheumatic Fever* (New York Commonwealth Fund 1940) p 21 Wilson has also recently summarized her views (Heredity and rheumatic disease" Am J Med 2 190 1947)

12 FOWLER J K On the association of affections of the throat with acute rheumatism Lancet 2:933 1880

The relation of hemolytic streptococcus sore throat to rheumatic fever is a relatively modern concept Indeed in the older literature one scans series after series of cases (Refs 3 4 and 5) without finding any allusion to sore throat at all Senator (Die Krankheiten des Bewegungsapparatus in Von Ziemssen *Handbuch der speciellen Pathologie und Therapie* [Leipzig F C W Vogel 1875] 13 12) for example in his comprehensive article makes no mention of sore throat Sutton s case (Ref 7) is an exception to the general rule When attention began to be centered on the throat and tonsils confusion arose since sore throats are mentioned with all sorts of bacteriological findings and in many cases rheumatic fever on the basis of the old theory of focal infection (F Billings Focal infection its broader application in the etiology of general disease" J A M A 63 899 1914) was attributed to septic tonsils that is to say tonsils which were simply large and which contained bacteria of all sorts We should make it clear that the current view of the relation of sore throat to rheumatic fever refers to a specific acute group A tonsillitis or pharyngitis even if mild Much of the older literature is therefore worthless it is comprehensively reviewed by David and Robert Thomson ("An historical survey of researches on the role of the streptococci in acute articular rheumatism or rheumatic fever G The association of tonsillitis with rheumatic fever and its manifestations" Ann Pickett Thomson Res Lab 4 [Pt 1] 56 1928)

Fowler is however quite clear on the subject "I have for some time past made it a rule in all cases of acute rheumatism to inquire carefully for any history of tonsillitis or catarrh of the pharynx having preceded the attack I was led to do this by a remark from Dr Garrod F R S when he was attending me for a severe attack of rheumatic fever in the winter of 1874 A month before my illness I had a sharp attack of acute tonsillitis and Dr Garrod told me he noticed that the two affections were not uncommonly associated Without at present being able to give an exact percentage of cases presenting this premonitory symptom I think I should not exaggerate if I were to put it at 80

per cent" Fowler proceeds to describe the details of 20 patients in whom a bad sore throat preceded evidence of articular rheumatism by intervals of 7–21 days This paper is a masterpiece of precise reporting and leaves no doubt as to the association of tonsillitis and rheumatic fever This association is discussed in detail in the elaborate "Reports of the Collective Investigative Committee of the British Medical Association" (Ref 13) Among 655 cases of articular rheumatism 158 were "the subjects of tonsillitis" One patient a woman aged thirty had had three attacks of tonsillitis "each followed by acute rheumatism" A Mantle ("The etiology of rheumatism from a bacterial point of view" Brit M J 1:1381 1887) later noted that "rheumatism and scarlatina were not infrequently observed in the same house scarlatina attacking the younger members of the family rheumatic fever the older scarlatina usually entering the house first Acute tonsillitis had frequently been observed under the same conditions" E Roos (Uber rheumatische Angina" Berl klin Wchnschr 31 575 1894) comments on the lack of recognition of this association in Germany and reports a case of typical tonsillitis followed in 12 days by acute arthritis He gives an excellent comprehensive review of the early literature on the subject as does E Bloch ("Zur Aetiologie des Rheumatismus" Munchen med Wchnschr 45 445 1898)

One of the most important points of all this work was the recognition of a latent period between the sore throat and the symptoms of rheumatic fever Later B Schick ("Über die Nachkrankheiten des Scharlach" Jahrb f Kinderh 1907 Ergänzungsband p 132) formulated the latent period between scarlet fever and its sequels as an allergic manifestation and while he mentioned postscarlatinal "rheumatism" as one of the sequels the evidence is that he did not identify such rheumatism with acute rheumatic fever but regarded it as a specific consequence of scarlatina This view was challenged on good evidence by J R Paul R Salinger and B Zuger ("The relation of rheumatic fever to post scarlatinal arthritis and post scarlatinal heart disease a familial study" J Clin Investigation 13 503 1934) Recently E E Fischel ("The role of allergy in the pathogenesis of rheumatic fever Am J Med 7 772 1949) has given a definitive review of this phase of the subject with a bibliography of nearly three hundred titles J K Aikawa ("Hypersensitivity and rheumatic fever" Ann Int Med 41 576 1954) also discusses the subject in interesting fashion

Turning now to more modern material J A Glover ("Incidence of rheumatic disease" Lancet 1 199 1930) tells of an interesting outbreak in a training school where two thousand boys lived in crowded quarters "There was a sharp epidemic of tonsillitis followed by an outbreak of acute rheumatism Again we see the peak of the tonsillitis epidemic precedes the crest of the rheumatic wave by some two or three weeks The situation was now getting "warm" as to incriminating in some way the hemolytic streptococcus A F Coburn and R H Pauli (Studies on the relationship of Streptococcus hemolyticus to the rheumatic process I Observations on the ecology of hemolytic streptococcus in relation to the epidemiology of rheumatic fever" J Exper Med 56 609 1932) were among the first to go further and insist on infection with hemolytic streptococcus "The majority of rheumatic patients who contract hemolytic streptococcus pharyngitis experience shortly afterward a definite recrudescence of their disease In conclusion there is a close relationship between respiratory

infection with hemolytic streptococcus and activity of the rheumatic process in susceptible individuals In another paper Coburn and Pauli ("Studies on the relationship of Streptococcus hemolyticus to the rheumatic process II Observations on the biological character of Streptococcus hemolyticus associated with rheumatic disease J Exper Med 56 633 1932) showed that the streptococci isolated from the throats of rheumatic persons were not of a single Lancefield type but fell into six antigenic groups

W R F Collis (Acute rheumatism and haemolytic streptococci " Lancet 1 1341 1931) quotes Dr F Griffith who investigated an outbreak of tonsillitis at a public school which was followed in several instances by primary acute rheumatism Griffith found that a haemolytic streptococcus of a well defined serological type was responsible for the cases and suggested (private communication) that there might be direct aetiological connexion between this streptococcal infection and rheumatic attacks " It is of interest in this connection that recent work has shown that post streptococcal nephritis almost always is preceded by Type 12 hemolytic streptococcal throat infection (C N Stetson C H Rammelkamp Jr R M Krause R J Kohen and W D Perry "Epidemic acute nephritis studies on etiology natural history and prevention " Medicine 34 431 1955) Collis himself showed in an epidemic of acute tonsillitis that rheumatic relapses occurred in 9 out of 11 children who developed acute *streptococcal infection while similar febrile disorders not associated with the* hemolytic streptococcus caused no relapse " J A Glover and F Griffith ("Acute tonsillitis and some of its sequels epidemiological and bacteriological observations Brit M J 2 521 1931) conclude that infection of the throat with hemolytic streptococci produces varying clinical pictures in different persons These include first a symptomless infection secondly tonsillitis thirdly febricula feverish catarrh or pharyngitis without noticeable sore throat Any of the latter three conditions may be followed by otitis media or by acute rheumatism " Glover in contrast to the American experience found most cases of scarlet fever to be caused by Types 1 2 3 and 4 W H Bradley ("Epidemic acute rheumatism in a public school Quart J Med 1 79 1932) reports on an interesting outbreak in a boys school "Two epidemics of rheumatism are recorded and their relation to parallel waves of hemolytic streptococcal sore throat are demonstrated the causal streptococci being of two distinct strains " L A Rantz working in the army camps on outbreaks of acute rheumatic fever during World War II confirmed and amplified the early observations (L A Rantz P J Boisvert and W W Spink "Etiology and pathogenesis of rheumatic fever " Arch Int Med 76 131 1945 and "Hemolytic streptococcic sore throat the post streptococcic state *ibid* 79:401 1947) Rantz and his associates found that the alleged latent period between throat infection and outburst of rheumatic fever was really featured by various abnormalities They worked out details of the streptococcal infection with reference to definition of strains and they designated all the non suppurative late events as the post streptococcic state" there were many other interesting findings

While attacks of acute rheumatism are then so often preceded by hemolytic streptococcus throat infections not all outbreaks of streptococcal tonsillitis are followed by rheumatic fever A L Bloomfield and A R Felty ("Bacteriological observations on acute tonsillitis with reference to epidemiology and susceptibility Arch Int Med 32 483 1923) for example studied with the

greatest care the clinical and bacteriological features of acute follicular tonsillitis in a closed group During one season there were 39 cases all caused by hemolytic streptococcus in not a single instance was there any evidence of rheumatic fever So too A L Bloomfield and L A Rantz ("An outbreak of streptococcic septic sore throat in an army camp" J A M A 121 315 1943) studied an outbreak of acute streptococcus sore throat affecting several hundred soldiers due to Type 15 hemolytic streptococcus Within three weeks there was no evidence of rheumatic fever in a single man Possibly the organisms involved were not "rheumatogenic"

13 WHIPHAM T Reports of the Collective Investigating Committee of the British Medical Association Report on Inquiry No III Acute rheumatism Brit M J 1:387 1888

The committee invited doctors to send in reports of cases of acute rheumatism observations on 655 patients were received These reports are analyzed from every conceivable standpoint and furnish a mine of information Some of the points discussed are sex, age occupation class in society habits food locality atmosphere antecedent tonsillitis antecedent scarlet fever chorea influence of treatment relapsing cases etc

14 CHEADLE W B Harveian lectures on the various manifestations of the rheumatic state as exemplified in childhood and early life Lancet 1:821 871 921 1889

We have already pointed out how the concept of rheumatic fever widened in scope from simple acute arthritis during the first three quarters of the century It remained for someone to organize and codify all this information and this Cheadle did in these lectures which are a landmark in the clinical study of the subject The material was published as a book *The Various Manifestations of the Rheumatic State as Exemplified in Childhood and Early Life* (London Smith, Elder & Co 1889) and later on in revised form in Cheadle s monograph *Occasional Lectures on the Practice of Medicine* (London Smith Elder & Co 1900)

Cheadle enumerates the various manifestations of the rheumatic state Endocarditis and pericarditis pleurisy and tonsillitis are seen in both adults and children Subcutaneous tendinous nodules chorea and exudative erythema are commoner in children "For my present purpose I shall assume the connexion and speak of these seven phases together with arthritis as the rheumatic series Each of these manifestations is systematically discussed with illustrative case reports "The account of the various phases of rheumatism would be incomplete without some reference to the scarlatinal affection Articular inflammation appears now and again in the course of scarlet fever which can in no way be distinguished from that of acute rheumatism It is often accompanied by endocarditis or pericarditis and sometimes by chorea" In this point of view Cheadle was far ahead of his time

T Duckett Jones ("The diagnosis of rheumatic fever" J A M A 126 481 1944) later classified the various manifestations of rheumatic fever from the standpoint of value in diagnosis He divided the criteria into major (carditis polyarthritis chorea subcutaneous nodules and erythema marginatum) and minor (fever arthralgia prolonged P R in the electrocardiogram preceding

hemolytic streptococcal infection previous rheumatic fever or inactive rheumatic heart disease) These criteria have been modified by the American Heart Association (*Modern Concepts of Cardiovascular Disease Jones Criteria* [Modified] *for Guidance in the Diagnosis of Rheumatic Fever* [1955] Vol 24 No 9)

15 NEWSHOLME A The natural history and affinities of rheumatic fever a study in epidemiology Lancet I 589 657 1895

"The thesis which will be advanced and supported is that rheumatic fever *is a specific febrile disease* caused by a pathogenic micro-organism Such a view of the causation of rheumatic fever does *not* cover the *entire* ground Assuming that rheumatic fever only occurs when a special pathogenic micro-organism is introduced its causation is by no means exhausted It occurs chiefly or only in predisposed persons in certain states of health and under the influence of certain excitants—as fatigue injury and chill the exact value of which in its causation will be hereafter discussed Further it occurs by preference at certain seasons of the year in certain localities or perhaps on certain soils We have to consider on the one hand the influences determining an individual attack of rheumatic fever and on the other hand the wider influences determining the extent of its varying prevalence in different countries in successive years"

A more precise statement of the problem could not be made today (1957) The following factors Newsholme regards as essential the active infective agent conditions of environment and personal factors He reviewed some earlier reports on "epidemic" outbreaks but concluded "There has however so far as I am aware been no wide and thorough investigation of the epidemiology of rheumatic fever" First Newsholme traced the incidence of rheumatic fever in various hospitals through the years and concluded that there was at times a definite epidemic prevalence then the influences of the various ancillary factors enumerated above are analyzed Newsholme felt that the influence of heredity had been exaggerated but that injury and fatigue were definite predisposing factors and that dust perhaps had some influence He also found a close relationship between rainfall level of ground water and the amount of rheumatic fever "There is abundant evidence of seasonal incidence of rheumatic fever"

Meanwhile A Hirsch (*Handbuch der historisch geographischen Pathologie* [2d ed Stuttgart Ferdinand Enke 1886] 3 530) gave a list of outbreaks from which he concluded that "polyarthritis is a specific infectious disease" The subject may be pursued further in the paper of D Seegal and B C Seegal ("Studies in the epidemiology of rheumatic fever" J A M A 89 11 1927) and in that of R M Atwater ("Studies in the epidemiology of acute rheumatic fever and related diseases in the United States based on mortality statistics Am J Hyg 7 343 1927) who concludes that "acute rheumatic fever appears to be related to the family of streptococcal infections because of bacteriological indications clinical resemblances and epidemiological kinship" The subject is dealt with fully and systematically by J R Paul (*The Epidemiology of Rheumatic Fever* [New York Metropolitan Life Insurance Co 1930] *The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects* [New York Metropolitan Life Insurance Co 1943]) Finally F F Schwentker

("The epidemiology of rheumatic fever" in *Rheumatic Fever* ed L Thomas [Minneapolis University of Minnesota Press 1952] p 17) gives a precise recent review

16 ASCHOFF L Zur Myocarditisfrage Verhandl d deutsch path Gesellsch 8 46 1904

William Stokes (*The Diseases of the Heart and Aorta* [Dublin Hodges & Smith 1854]) clearly recognized disease of the heart muscle as of importance apart from valve lesions (pp 109 and 113) There are also a number of hints in the early literature as to the presence of anatomical myocardial changes in cases of rheumatic fever S West ("Analysis of 40 cases of rheumatic fever" St Bart s Hosp Rep 14:221 1878) for example stated in regard to dilatation of the heart "This may depend upon organic changes in the muscular tissue and in one case was proved to do so by microscopical examination" which showed that "in these white patches the muscular tissue had undergone acute granular (fatty) degeneration its fibers being converted into granular cylinders" In James F Goodhart s case of rapid enlargement of the heart (Tr Path Soc London 30 279 1879) myocardial changes were found also "I examined sections of the muscular wall microscopically and there was a considerable quantity of interstitial cell growth around the vessels and between muscular fasciculi" But these observations were highly rudimentary and it was L Krehl ("Beitrag zur Pathologie der Herzklappenfehler" Deutsches Arch f klin Med 46 454 1890) and E Romberg ("Uber die Bedeutung des Herzmuskels fur die Symptome und den Verlauf der acuten Endocarditis und der chronischen Klappenfehler Deutsches Arch f klin Med 53:141 1894) who were pioneers in emphasizing the importance of the anatomical and functional state of the myocardium apart from valve lesions While they did not describe the specific lesion of rheumatic fever they did stress changes in the myocardium as a result of rheumatic fever and other infections

It was Aschoff however who first described the specific rheumatic lesion in the myocardium—the Aschoff body "We succeeded in defining more closely the histological makeup of the products of inflammation and indeed in finding peculiar nodules which seem to be specific for rheumatic myocarditis To be sure full blown nodules were found in only two cases of recurring endocarditis but they correspond in their situation with the cellular proliferation found in the other cases They are regularly situated in the vicinity of small or medium blood vessels and often show an intimate relation to the adventitia Or there may be a lesion of all the vessel coats such as is described in arteritis nodosa The actual nodules are very small submiliary and consist of the approximation of strikingly large cells with one or more abnormally large slightly indented or polymorphous nuclei He goes on in much more detail "While in one case the nodule makes the impression of a fresh cell proliferation in another a partial or total fibrous change can be demonstrated" Aschoff strongly supported the Leipzig school—Krehl and Romberg—in their contention that cardiac failure was due more to weakness resulting from changes in the myocardium than from valve lesions

P Geipel soon confirmed Aschoff's findings (Untersuchungen uber rheumatische Myokarditis" Deutsches Arch f klin Med 85 75 1905) as did C Coombs ("The myocardial lesions of the rheumatic infection Brit M J

8 1513 1907) in England Meanwhile Aschoff ("A discussion of some aspects of heart block" Brit M J 2 1103 1906) described the nodules in English E Bracht and Wachter ("Beitrag zur Aetiologie und pathologische Anatomie der Myocarditis rheumatica Deutsches Arch f klin Med 96 493 1909) found the nodules in three cases of definite acute rheumatism but in no patient dying of other infectious diseases Finally W Thalhimer and M A Rothschild ("On the significance of the submiliary myocardial nodules of Aschoff in rheumatic fever" J Exper Med 19 417 1914) reviewed the literature and reported their own studies They regarded the nodules as characteristic of rheumatic infection and even in the absence of a rheumatic history believed that the presence of Aschoff bodies signified a previous attack of rheumatism The nodules were found in three cases of chorea proving the close relation of this condition to rheumatism Thalhimer and Rothschild found the nodules most often in the walls of the left ventricle where infection antedated death by a long period fresh Aschoff bodies were not always in evidence but the healed remains represented by sclerotic patches were present C McEwen ("Cytological studies on rheumatic fever I The characteristic cell of the rheumatic granuloma J Exper Med 55 745 1932) later studied by supravital stains material aspirated from subcutaneous fibroid nodules He concluded that the characteristic large cells "probably arise from the undifferentiated mesenchymal elements of loose connective tissue although it is possible that endothelial cells take part in their formation in some instances Since there is little doubt that the subcutaneous rheumatic nodules are pathologically identical with rheumatic granulomata elsewhere in the body these conclusions are considered applicable also to the Aschoff body cells of the myocardial submiliary nodules" But the subject has continued in dispute and recently G F Murphy ("Evidence that Aschoff bodies of rheumatic myocarditis develop from injured myofibers J Exper Med 95 319 1952) sustained the thesis that the essential lesion appeared to be "damaged muscle fibers their fragments and syncitial cell masses of probable muscular origin that proliferate from beneath the sarcolemma"

Other important general articles on the Aschoff body are those of W C von Glahn ("Auricular endocarditis of rheumatic origin" Am J Path 2 1 1926) and of B J Clawson ("The Aschoff nodule" Arch Path 8 664 1929) The latter has an extensive review of the literature

This may also be the appropriate spot to refer to the somewhat disputed subject of rheumatic arterial lesions (O Klotz "Arterial lesions associated with rheumatic fever" J Path & Bact 18 259 1913 A M Pappenheimer and W C von Glahn "Lesions of the aorta associated with acute rheumatic fever and with chronic cardiac disease of rheumatic origin J M Res 44 489 1924)

17 FABER H K Experimental arthritis in the rabbit a contribution to the pathogeny of arthritis in rheumatic fever J Exper Med 22 615 1915

This time as we have pointed out (Ref 23) was the era of isolation of non hemolytic streptococci from cases of rheumatic fever and the production of lesions in rabbits with them Faber noted that in the literature especially when strains of low virulence were used there was a latent period between the injection of organisms and the occurrence of arthritis or it might even be necessary

to give more than one injection to produce disease He therefore thought that perhaps the joint needed to be prepared or "sensitized" by a preliminary contact with the antigen before an arthritic reaction could take place He showed experimentally that streptococci of "low virulence were frequently not able to produce arthritis at the first attack but at this time prepare the way for such an effect in a later attack" It was found that the exciting injection must be the same as that used for the sensitizing injection and furthermore that the preparation might be made by the introduction directly into the joint of organisms living or dead By intravenous inoculation without previous sensitization it was possible to cause arthritis in rabbits only after three or more injections An analogy between these experiments and the relapses of human rheumatic fever was suggested as well as a further analogy with the primary lesion in human rheumatic fever

H F Swift and R H Boots ("The question of sensitization of joints with non hemolytic streptococci" J Exper Med 38 573 1923) did not however confirm Faber s work They concluded that joints of rabbits first treated with streptococci "were no more liable to involvement than were other untreated joints of the same animals"

18 COHN A E and SWIFT H F Electrocardiographic evidence of myocardial involvement in rheumatic fever J Exper Med 39 1 1924

Disturbance of cardiac mechanism especially prolongation of conduction time occurs so frequently in rheumatic fever that Jones (Ref 14) sets it down as one of the minor diagnostic criteria J Parkinson A H Gosse and E B Gunson ("The heart and its rhythm in acute rheumatism" Quart J Med 13 363 1919) reviewed the literature on disturbances of cardiac mechanism in rheumatic fever and reported observations on 50 cases of their own which were studied clinically and with polygraphic tracings They described various disorders But Cohn and Swift first dealt with the subject comprehensively with electrocardiographic studies They found that "in one way or other the heart was affected in 35 of 37 cases of rheumatic fever" A V block occurred in eight cases and was the most frequent disturbance next to premature auricular contractions Such observations have now become standard practice in the study of acute rheumatic fever (L A Rantz P J Boisvert and W W Spink "Hemolytic streptococcic sore throat the poststreptococcic state Arch Int Med 79 401 1947)

19 SWIFT H F The pathogenesis of rheumatic fever J Exper Med 39 497 1924

Physicians had gradually recognized the association of a variety of apparently unrelated disturbances (Ref 14) with classical acute articular rheumatism endocarditis pericarditis myocarditis chorea subcutaneous fibroid nodules and other lesions Swift in this important paper brought out and pictured an identity of the underlying pathological changes in all these various manifestations "The perivascular proliferative type of lesion resembling an infectious granuloma explains the subacute and chronic character of the clinical symptoms in many patients with this disease Marked exudation of serum into the peri articular tissues and of serum and cells into the joint cavities are concomitants of the acute arthritis A short while later there appeared the authoritative re

view of W G MacCallum (Rheumatism" J A M A 84 1545 1925) with a brilliant description of the lesions including the diffuse rheumatic changes in the left auricle to which he first drew attention ("Rheumatic lesions of the left auricle of the heart" Bull Johns Hopkins Hosp 35 329 1924) In 1940 Swift (Rheumatic heart disease pathogenesis and etiology in their relation to therapy and prophylaxis Medicine 19 417 1940) developed the whole subject further Other comprehensive reviews of the pathological changes are those of B Sacks (Pathology of rheumatic fever a critical review" Am Heart J 1 750 1926), of W C von Glahn ("The pathology of rheumatism" Am J Med 2 76 1947), and of G E Murphy (The histopathology of rheumatic fever a critical review" in *Rheumatic Fever* ed L Thomas [Minneapolis University of Minnesota Press, 1952] p 28) These articles have extensive bibliographies

20 SWIFT H F Rheumatic fever J A M A 92 2071 1929

In this masterly lecture Swift brings every phase of acute rheumatic fever—clinical variations pathology etiology—up to date He touches on his own hypothesis of hypersensitivity to non hemolytic streptococci

21 PAUL, J R Pleural and pulmonary lesions in rheumatic fever Medicine 7 383 1928

Paul reviews critically this whole somewhat confused and indefinite subject and *more recently E E Muirhead and A E Haley* (Rheumatic pneumonitis Arch Int Med 80 328 1947) again go over the question and report anatomical studies of their own

22 COBURN A F The factor of infection in the rheumatic state Baltimore Williams & Wilkins Co 1931

Modern views on rheumatic fever at least in America were much influenced by Coburn s book Instead of a narrow concept of acute rheumatic fever he looked on the disease from a wider aspect as the rheumatic state" Thus under this head he included a great variety of manifestations the significance of some of which was not generally recognized While Coburn s spectrum is perhaps too broad he deserves credit for expanding the older narrow limits of the disease All sorts of material—environmental bacteriological—are discussed in detail Coburn also deserves credit for being one of the first to point the finger at the hemolytic streptococcus as a specific causal agent (see also Ref 12)

But as one goes back in the literature one usually finds that things have been said before and it must be stated that Coburn s views on the natural history of the disease were anticipated by Cheadle (Ref 14) who actually used the term the rheumatic state"

23 LICHTMAN S S and GROSS L Streptococci in the blood in rheumatic fever *rheumatoid arthritis and other diseases* based on a study of 5 233 consecutive blood cultures Arch Int Med 49 1078 1932

It was inevitable that with the advent of the bacteriological era a disease like rheumatic fever should be regarded as due to a living agent The long series of reports of cultivation of various organisms from patients with rheumatic fever or at autopsy is thoroughly summarized by David and Robert Thomson ("An

historical survey of researches on the role of the streptococci in acute articular rheumatism or rheumatic fever" Ann Pickett Thomson Res Lab 4:1 1928) and only a few can be listed in this bibliography Throughout the history of the subject however three errors constantly recur First, undoubtedly there was often confusion between acute rheumatic fever and subacute bacterial endocarditis streptococci isolated from cases of the latter condition were often as signed as the cause of rheumatic fever Second there was at the time no realiza tion that non hemolytic streptococci are basic members of the normal flora of the throat and bowel and that they may on occasion be isolated from the blood of healthy people Third it was not realized that any streptococcus injected in travenously into rabbits in adequate dosage may produce multiple lesions of joints and of endocardium Observations of this sort were used as arguments that organisms isolated from patients were the cause of rheumatic fever R I Cole (Experimental streptococcus arthritis in relation to the etiology of acute articular rheumatism" J Infect Dis 1:714 1904) early pointed out the latter error First, he reported his own work to the effect that over a three year period cultures from blood and joint effusions in every case of rheumatic fever seen in the Johns Hopkins Hospital were sterile He then injected into rabbits strains of streptococci from sources definitely not rheumatic and concluded "Arthritis and endocarditis may be produced by the intravenous inoculation of rabbits with streptococci from various sources and the results obtained are quite similar to those described as resulting from the inoculation of the so-called Micrococcus or Diplococcus rheumaticus Therefore the description of a distinct variety or species of streptococci based on this property of causing endocarditis and arthritis [in rabbits] is unwarranted"

A few of the early bacteriological claims must however be listed because of their importance in the history of the subject F J Poynton and A Paine ("The etiology of rheumatic fever" Lancet, 2 861 932 1900) cultivated from blood and joints in eight cases of rheumatic fever a Gram positive coccus with which they produced lesions in rabbits This work drew wide attention and served for some years as a focal point for discussion of the etiology of rheumatic fever Poynton and Paine finally embodied all their work in a volume entitled *Re searches on Rheumatism* (London J & A Churchill Ltd 1913) It is of inter est that years later Poynton gave ground from his strong position doubted that a streptococcus was the sole cause of rheumatic fever and suggested looking elsewhere—for example for a filter passer ("The prevention of acute rheumatism Lancet, 2:1000 1924) H F Swift and R A Kinsella ("Bacteriological studies in acute rheumatic fever" Arch Int Med 19 381 1917) were able to culti vate non hemolytic streptococci from somewhat less than 10 per cent of typical cases of acute rheumatic fever They concluded with the rather vague statement that "it seems evident that no type of streptococcus has been constantly asso ciated with acute rheumatic fever B J Clawson ("Studies on the etiology of acute rheumatic fever J Infect Dis 36 44 1925) using large amounts of blood (50 cc) for culture isolated non hemolytic streptococci from a consider able percentage of cases of acute rheumatic fever and produced lesions in rab bits He erroneously thought that "rheumatic endocarditis and subacute bac terial endocarditis may be produced by the same agent and are but different degrees of the same process" Similarly J C Small ("The bacterium causing rheumatic fever and a preliminary account of the therapeutic action of its

specific antiserum Am J M Sc 173 101 1927) described the isolation of "a serologically specific nonhemolytic streptococcus with distinctive biological characteristics from blood and throats of patients with rheumatic fever with this organism he produced the usual rabbit lesions We therefore have named this microorganism Streptococcus cardioarthritidis and offer it upon the basis of these observations as the cause of rheumatic fever Finally R L Cecil E E Nicholls and W J Stainsby (Bacteriology of the blood and joints in rheumatic fever J Exper Med 50 617 1929) were able to cultivate strepto cocci from the blood in the amazingly high figure of 83 9 per cent of cases These findings corroborate those of previous investigators and make it difficult to escape the conclusion that rheumatic fever is a streptococcal infection usually of the alpha or viridans type

Interestingly enough R N Nye and E Waxelbaum (Streptococci in infec tious [atrophic] arthritis and rheumatic fever J Exper Med 52 885 1930) following Cecil Nicholls and Stainsbys technique with meticulous care were unable to confirm their results

On the other side of the argument R N Nye and D Seegal (Non hemo lytic streptococci and acute rheumatic fever J Exper Med 49 539 1929) found that blood cultures from 25 cases of acute rheumatic fever were negative for non hemolytic streptococci They emphasized quite properly that non hemo lytic streptococci are invariably present in immeasurable numbers in the throats of all human beings and that their cultivation from the throats of rheumatic fever patients is meaningless The foregoing facts seem to invalidate the as *sumption that any of these non hemolytic streptococci play a specific role* in the etiology of acute rheumatic fever Another blow was struck by L Gross L Loewe and B Eliasoph (Attempts to reproduce rheumatic fever in animals" J Exper Med 50 41 1929) who claimed that streptococci isolated from rheumatic fever did not produce true lesions of the disease (Aschoff bodies) in rabbits Judged by these criteria we have failed to reproduce the disease This conclusion we believer holds true for all the work thus far reported in the literature It remained for Lichtman and Gross with a truly devastating attack to demolish the theory that rheumatic fever was a direct infection with non hemolytic streptococci They began by listing 11 major fallacies in the previous work and concluded that study of 5 233 consecutive blood cultures shows [that] an incidence of non hemolytic streptococcemia between 4 and 15 5 per cent occurs in at least 9 diseases some of which such as aplastic anemia anemia leukemia and colitis obviously had nothing to do with rheumatic fever On the basis of the incidence of the transient streptococcemia *alone* these organisms cannot justifiably be considered causative agents of these dis eases"

Thus at long last the ghost of this controversy which had been waged for forty years was finally laid

24 MYERS W K and KEEFER C S Antistreptolysin content of the blood serum in rheumatic fever and rheumatoid arthritis J Clin Investi gation 13 155 1934

Since hemolytic streptococcal throat infections were often found to precede bouts of acute rheumatic fever it was natural to look for antibodies against streptococci or their products in the blood serum of patients B Schlesinger and

A G Signy ("Precipitin reactions in the blood of rheumatic patients following acute throat infections" Quart J Med 2 255 1933) for example studied precipitin reactions and C S Keefer W K Myers and T W Oppel (Streptococcal agglutinins in patients with rheumatoid [atrophic] arthritis and acute rheumatic fever" J Clin Investigation 12 267 1933) measured agglutinins The determination of antistreptolysin titer has remained the popular method however of investigating antibodies against hemolytic streptococcus E W Todd ("Antihaemolysin titres in haemolytic streptococcal infections and their significance in rheumatic fever" Brit J Exper Path 13 248 1932) made early studies as did A F Coburn and R Pauli ("Studies on the relationship of Streptococcus hemolyticus to the rheumatic process III Observations on the immunological responses of rheumatic subjects to hemolytic streptococcus J Exper Med 56:651 1932) Both these groups of workers found increased titers of antistreptolysin during acute attacks of rheumatic fever The observations of Myers and Keefer are however of special interest because of the large number of controls Thus they found that the antistreptolysin serum levels of patients with rheumatic fever fell in the same range as those with overt hemolytic streptococcal infections such as scarlet fever and erysipelas and that these levels were often higher than ever attained in normal persons However many patients with rheumatic fever had titers not above those reached in normals J J Bunim and C McEwen ("The antistreptolysin titer in rheumatic fever arthritis and other diseases" J Clin Investigation 19 75 1940) found that the "incidence of elevated titers bore no relation to the various clinical manifestations of rheumatic infection but those whose illness was preceded by a memorable upper respiratory infection showed a response more commonly than those without such a history

Through the years stress has been placed on abnormally high titers as an indication of hemolytic streptococcal infection or of rheumatic fever in doubtful cases where there is no overt sore throat or positive culture for a hemolytic streptococcus L A Rantz (*Rheumatic Fever* [Chicago Year Book Publishers Inc 1954]) finds antistreptolysin measurements most useful for the exclusion of rheumatic fever It is evident that titers of 50 units or less are virtually incompatible with the early stages of rheumatic fever Rantz and his group have reported other important studies on antistreptolysin (L A Rantz, M Maroney and J M Di Caprio Antistreptolysin O response following hemolytic streptococcus infection in early childhood" Arch Int Med 87 360 1951 L A Rantz E Randall and H H Rantz "Antistreptolysin O a study of this antibody in health and in hemolytic streptococcus respiratory disease in man Am J Med 5 3 1948) Numerous other antistreptococcal antibodies have been studied to the same general effect but their use has not yet become feasible in routine clinical work (L A Rantz *The Prevention of Rheumatic Fever* [Springfield Ill Charles C Thomas 1952] pp 16 ff) The earlier work is also reviewed by Wilson (*Rheumatic Fever* [New York Commonwealth Fund 1940] pp 96 ff) Other serological tests not including streptococcal antibodies have been suggested Their use is reviewed by M McCarty ("Present status of diagnostic tests for rheumatic fever Ann Int Med 37 1027 1952) A penetrating analysis of this phase of the subject is also given by H F Swift ("The etiology of rheumatic fever Ann Int Med 31 715 1949) by R A Good ("Acute phase reactions in rheumatic fever" in *Rheumatic Fever* ed L

Thomas [Minneapolis University of Minnesota Press 1952] p 115) and by M McCarty (The immune response in rheumatic fever [*ibid* p 136])

Recently stress has been placed on tests which may reveal the "activity" of the rheumatic process Such a test is the measurement of C-reactive protein in the blood G H Stollerman S Glick D J Patel I Hirschfeld and J H Rusoff (Determination of C reactive protein in serum as a guide to the treat ment and management of rheumatic fever" Am J Med **15** 645 1953) and R J Roantree and L A Rantz (Clinical experience with the C reactive protein test Arch Int Med **96** 674 1955) attempt to evaluate this test upon which the last word is not yet said The subject is summarized editorially by J J Bunim (Laboratory tests for rheumatic activity [editorial] J Chronic Dis **3** 230 1956)

25 COBURN A F and MOORE L V The prophylactic use of sulfanilamide in streptococcal respiratory infections with special reference to rheumatic fever J Clin Investigation **18** 147 1939

Having found that sulfanilamide used prophylactically prevented the development of induced hemolytic streptococcal infections in guinea pigs even though it did not cure them when established it occurred to Coburn and Moore to see whether the drug had any prophylactic effect against rheumatic fever in children Seventy nine of eighty rheumatic children escaped "hemolytic streptococcal infection and sign of rheumatic activity" while under treatment C B Thomas and R France (A preliminary report of the prophylactic use of sulfanilamide in patients susceptible to rheumatic fever Bull Johns Hopkins Hosp **64** 67 1939) and C B Thomas R France and F Reichsman (The prophylactic use of sulfanilamide in patients susceptible to rheumatic fever J A M A **116** 551 1941) reported similar favorable results No major rheumatic episodes occurred during the 79 person seasons in the treated group whereas there were 10 per cent recurrences in the controls A G Kuttner and G Reyersbach ("The prevention of streptococcal upper respirotory infections and rheumatic recurrences in rheumatic children by the prophylactic use of sulfanilamide" J Clin Investigation **22** 77 1943) strongly supported the above findings as did R H Feldt (Sulfanilamide as a prophylactic measure in recurrent rheumatic infection a controlled study involving 131 patient seasons Am J M Sc **207** 483 1944) C R Messeloff and M H Robbins ("Prophylactic use of sulfonamides in children with rheumatic fever" J Lab & Clin Med **28**:1323 1943) on the other hand failed to find a significant difference between the test group and the controls A J Morris R Chamovitz F J Catanzaro and C H Rammelkamp Jr (Prevention of rheumatic fever by treatment of previous streptococcic infections effect of sulfadiazine" J A M A **160**:114 1956) found that the treatment of the acute sore throat with sulfadiazine neither eradicated the streptococcus nor prevented subsequent rheumatic fever However they regarded sulfonamides as of value in prophylaxis

All this work has now become rather a dead issue because sulfonamides have been almost universally replaced by penicillin (Ref 27) but it served to bring out a principle in the prophylaxis of rheumatic fever which is generally recognized as sound—the prevention of hemolytic streptococcus throat infections pro-

tects against the evidences of rheumatic fever which so often follow such infection

26 RICH A R and GREGORY J E Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity Bull Johns Hopkins Hosp 73 239 1943

We have already referred to the concept of hypersensitivity in rheumatic fever (Ref 12) The observations of Rich and Gregory seem however particularly striking "The experimental procedure in this study has consisted in the sensitization of rabbits to sterile horse serum under conditions that produce serum sickness" They picture beautiful lesions that "in their basic characteristics resemble closely those of rheumatic carditis" In a further paper Rich and Gregory (Further experimental cardiac lesions of the rheumatic type produced by anaphylactic hypersensitivity" Bull Johns Hopkins Hosp 75:115 1944) show side by side experimental lesions and the lesions of human rheumatic carditis they appear practically identical S D Kobernick ("Experimental rheumatic carditis periarteritis nodosa and glomerulonephritis" Am J M Sc 224 329 1952) gives a comprehensive review of the entire subject with full bibliography

27 MASSELL B F DOW J W and JONES T D Orally administered penicillin in patients with rheumatic fever J A M A 138 1030 1948

The authors report pioneer observations of the effect of penicillin on hemolytic streptococcus carriage in the throat Orally administered penicillin in doses of 300 000–1 000 000 units per day for 10 days suppressed hemolytic streptococci in the throats of all but 2 1 per cent of patients with rheumatic fever Many papers soon followed describing all sorts of permutations and combinations of methods of administration dosage and type of preparation of penicillin Some of the important reports are the following F W Denny L W Wannamaker W R Brink C H Rammelkamp Jr and E A Custer "Prevention of rheumatic fever" J A M A 143 151 1950 L W Wannamaker C H Rammelkamp Jr F W Denny W R Brink H B Houser E O Hahn and J H Dingle "Prophylaxis of acute rheumatic fever by treatment of the preceding streptococcal infection with various amounts of depot penicillin" Am J Med 10 673 1951 B F Massell G P Sturgis J D Knobloch R B Streeper T N Hall and P Norcross Prevention of rheumatic fever by prompt penicillin therapy of hemolytic streptococcic respiratory infections" J A M A 146 1469 1951 B B Breese chairman "Prevention of rheumatic fever" in *Modern Concepts of Cardiovascular Disease* (1953) Vol 22 No 1 R L Chancey A J Morris R H Conner F J Catanzaro R Chamovitz, and C H Rammelkamp Jr "Studies of streptococcal prophylaxis comparison of oral penicillin and benzanthine penicillin" Am J M Sc 229 165 1955 and finally G H Stollerman J H Rusoff and I Hirschfeld Prophylaxis against group A streptococci in rheumatic fever New England J Med 252 787 1955 Stollerman observed no recurrences among 145 patients with rheumatic fever who received monthly injections of benzanthine penicillin during a 2 year period As a result of all this work the various heart associations are now urging that children who have had evidence of rheumatic fever receive penicillin pro

phylaxis over long periods The final details of this procedure are not yet defined

The whole subject of prevention of rheumatic fever is critically discussed in L A Rantz *The Prevention of Rheumatic Fever* (Springfield Ill Charles C Thomas 1952)

28 MURPHY G E and SWIFT H F *Induction of cardiac lesions closely* resembling those of rheumatic fever in rabbits following repeated skin infections with group A streptococci J Exper Med **89** 687 1949

Although Faber's views (Ref 17) demand some modification in the light of recent work he deserves credit for opposing the idea that rheumatic fever was a simple direct infection with streptococci and for promoting the concept of altered reactivity (allergy) in the mechanism of production of the clinical phenomena of the disease

We must now turn to the work of Swift since it dominated the stage in America for many years Swift too regarded hypersensitivity as implicit in the reaction of rheumatic fever and with his associates developed a hypothesis which they formulated as follows The theory is advanced that the pathogenesis of rheumatic fever can be explained by the existence in certain individuals of a condition of hypersensitiveness (allergy or hyperergy) to streptococci *resulting from repeated low grade infections or from the persistence of foci of* infection in the body When under suitable circumstances streptococci or products of streptococci are disseminated to the tissues these tissues over react and the characteristic picture of the disease results (H F Swift C L Derick and C H Hitchcock Rheumatic fever as a manifestation of hypersensitiveness [allergy or hyperergy] to streptococci Tr A Am Physicians *43 192 1928*) In another paper (Bacterial allergy [hyperergy] to nonhemolytic streptococci in its relation to rheumatic fever J A M A 90 906 1928) these writers further set forth their hypothesis and express the feeling that reactions which have been ascribed to hemolytic streptococci were not obtained in their experiments

It would serve no purpose to give in detail the analogies with syphilis and tuberculosis upon which Swift's hypothesis was based or to recite the experimental evidence with which Swift and his associates sought to support their views during the next decade A list of the principal papers is as follows C L Derick and H F Swift Reaction of rabbits to non hemolytic streptococci I General tuberculin like hypersensitiveness allergy or hyperergy following the secondary reaction J Exper Med 49 615 1929 C H Hitchcock and H F Swift Studies on indifferent streptococci III The allergizing capacity of different strains J Exper Med 49 637 1929 H F Swift and C L Derick Reactions of rabbits to non hemolytic streptococci II Skin reactions in intravenously immunized animals J Exper Med 49 883 1929 H F Swift C H Hitchcock C L Derick, and Currer McEwen Intravenous vaccination with streptococci in rheumatic fever Am J M Sc **181** 1 1931 C L Derick and M N Fulton "Skin reactions of patients and normal individuals to protein extracts of streptococci J Clin Investigation **10** 121 1931 M P Schultz and H F Swift, "Reactions of rabbits to streptococci comparative sensitizing effect of intracutaneous and intravenous inocula in minute doses J Exper Med 55 591 1932

The obvious error in interpretation of this work is that while Swift and his associates clearly produced evidence of allergic reactions to non hemolytic streptococci and their products they did not produce rheumatic fever

But by 1940 Swift seemed to have modified his views on the relation of non hemolytic streptococci to rheumatic fever (Rheumatic heart disease pathogenesis and etiology in their relation to therapy and prophylaxis " Medicine 19 417 1940) He now inclined to the hemolytic streptococcus as the causal agent "At present the hemolytic streptococcus seems to bear a more intimate relationship to the disease than any other known pathogenic agent He referred to outbreaks of tonsillitis followed by rheumatic fever (Ref 12) Later Swift ("The relationship of streptococcal infections to rheumatic fever " Am J Med 2:168 1947) spoke out even more strongly for hemolytic streptococcus on the basis of patients with scarlet fever who later developed evidence of rheumatic fever The investigations of Swift culminated in his important work with Murphy They found that rabbits after sustaining two to ten infections with hemolytic streptococci of different serological types within 3–20 months sickened and developed various symptoms "In the hearts of the infected rabbits there have been found on microscopic examination focal alterations in the connective tissue framework in blood vessel adventitia valves mural endocardium epicardium and in the myocardial interstitium " These and other lesions closely resembling those found in rheumatic fever have developed in rabbits that sickened following multiple successive skin infections with several serological types of Group A streptococci " The lesions are beautifully pictured Finally a most interesting report is that of R J Glaser W A Thomas S J Morse and J E Darnell Jr "The incidence and pathogenesis of myocarditis in rabbits after group A streptococcal pharyngeal infections " J Exper Med 103:173 1956 These workers devised a method of producing acute streptococcal pharyngeal infections in rabbits which in many cases were followed by myocardial lesions thought to be typical of rheumatic fever When intradermal infections with the same organism were produced the lesions appeared in a much smaller number of animals

29 HENCH P S SLOCUMB C H BARNES A R SMITH H L POLLEY H F and KENDALL E C The effects of the adrenal cortical hormone 17 hydroxy 11-dehydrocorticosterone (compound E) on acute phase of rheumatic fever preliminary report Proc Staff Meet Mayo Clin 24 277 1949

Hench and his associates first observed that cortisone had favorable effects on rheumatic fever This brief report was promptly followed by extensive use both of cortisone and of corticotropin (ACTH) in other cases of the disease Within a year it was possible for B F Massell J E Warren G P Sturgis B Hall and E Craige ("The clinical response of rheumatic fever and acute carditis to ACTH New England J Med 242 641 1950) to make an extensive report on the subject In general the results were favorable although on long usage the untoward effects of adrenal steroids manifested themselves Reports now came in rapidly some of the important ones were the following M G Wilson and H N Helper "Effect of pituitary adrenocorticotropic hormone [ACTH] in acute rheumatic carditis J A M A 145 133 1951 T N Harris W B Abrams T F P Leo and J P Hubbard Cortisone therapy in acute rheumatic

carditis preliminary observations Circulation 3 215 1951 A G Kuttner J S Baldwin C McEwen J J Bunim M Ziff and D K Ford "Effect of ACTH and cortisone on rheumatic carditis J A M A 148 628 1952 and A R Barnes The effects of cortisone and ACTH on the acute phase of rheumatic fever Circulation 3 770 1951 A Golden and J W Hurst ("Alterations of the lesions of acute rheumatic myocarditis during cortisone therapy Circulation 7 218 1953) reported the changes in the cardiac lesions of a patient dying with acute rheumatic heart disease treated with cortisone An inhibition of the inflammatory reaction was found without demonstrable alteration of the collagen injury So too L M Taran G A Culotta N Szilagyi J M Jablon and W K Lane ("Effect of cortisone and ACTH on the protracted phase of rheumatic carditis in children Am J Med 14 275 1953) found that the exudative manifestations responded readily so long as therapy was maintained but that there was no convincing indication of definite arrest of active carditis B F Massell (Medical progress ACTH and cortisone therapy of rheumatic fever and rheumatic carditis New England J Med 251 183 221 263 1954) carefully reviews the entire literature to date He points out that the original hope of a total rapid cure of rheumatic fever by steroid therapy is not to be realized whereas a suppression of various inflammatory components of the disease may be achieved—especially fever and polyarthritis Finally a report by the United Kingdom and United States co operative group (The treatment of acute rheumatic fever in children a cooperative clinical trial of ACTH cortisone and aspirin" Circulation 11 343 1955) concludes "There was no evidence that any of the three agents resulted in uniform termination of the disease and on all treatments some patients developed fresh manifestations during treatment At the end of one year there was no significant difference between the three treatment groups in the status of the heart The use of steroids is therefore (January 1957) still *sub judice*

30 PINNIGER J L *The left auricular appendage in mitral stenosis a study of 15 cases submitted to valvulotomy* St Thomas s Hosp Rep 7 ser 2 54 1951

It had come to be generally accepted not only that the Aschoff body was evidence of the rheumatic state but that "fresh" looking nodules indicated an active" stage of the disease With the development of mitral valvulotomy for mitral stenosis there came into vogue the excision of the tip of the auricular appendage partly for purposes of biopsy Pinniger was the first to report examinations of auricular appendages removed at operation Aschoff node formation was present in no fewer than 10 (65 per cent) of these cases These findings give strong support to the view that activity of the rheumatic process persists in a high proportion of patients with clinically quiescent rheumatic valvular disease A little later M Kuschner M I Ferrer R M Harvey and R H Wylie ("Rheumatic carditis in surgically removed auricular appendages Am Heart J 43:286 1952) found Aschoff bodies in 4 of appendages excised in 11 patients who were clinically regarded as definitely inactive D Sabiston and R H Follis Jr (Lesions in auricular appendages removed at operations for mitral stenosis of presumed rheumatic origin" Bull Johns Hopkins Hosp 91 178 1952) made similar studies of the material from Blalock s clinic and also found the histological changes of rheumatic fever in a number of cases Of

particular significance would appear to be the discovery of such changes in patients who did not give a history of ever having had symptoms of a rheumatic episode" Similarly J P Decker C Van Z Hawn and S L Robbins found Aschoff bodies in 83 of 183 excised auricular appendages ("Rheumatic activity as judged by the presence of Aschoff bodies in auricular appendages of patients with mitral stenosis I Anatomic aspects" Circulation 8:161 1953) Review of the clinical records of these patients by W F McNeely L B Ellis and D E Harken ("Rheumatic activity as judged by the presence of Aschoff bodies in auricular appendages of patients with mitral stenosis II Clinical aspects" Circulation 8:337 1953) showed no correlation between the presence of Aschoff bodies and the usual clinical or laboratory criteria of rheumatic activity Finally J R Gil H Rodriguez and J J Ibarra ("Incidence of asymptomatic active rheumatic cardiac lesions in patients submitted to mitral commissurotomy and the effect of cortisone on these lesions" Am Heart J 50 912 1955) concluded from similar findings that "a large group (60 per cent) of patients submitted to commissurotomy show active but asymptomatic cardiac lesions"

But is there not another possible interpretation of all these findings? If Aschoff bodies are frequently found in patients with no evidence of rheumatic activity are the nodules absolutely reliable evidence of such activity? This thought would seem to be supported by the observations of W A Thomas J H Averill B Castleman and E F Bland ("The significance of Aschoff bodies in the left atrial appendage" New England J Med 249 761 1953) who found that "the Aschoff lesions and other histological changes in the atrial appendage of patients with fatal rheumatic fever are identical with those found in the surgical specimens from patients with mitral stenosis who show no recognizable clinical or laboratory signs of recent rheumatic activity" even though the authors themselves draw the opposite conclusion

31 SOLOFF L A ZATUCHINI J JANTON O H O'NEILL, T J E and GLOVER R P Reactivation of rheumatic fever following mitral commissurotomy Circulation 8 481 1953

The writers give a systematic description of the "postcommissurotomy" syndrome The syndrome occurred in 24 per cent of 179 consecutive persons subjected to the operation It is characterized by precordial pain and by fever is frequently associated with the precipitation or intensification of heart failure and is at times accompanied by migratory joint pains arrhythmias hemoptysis or psychosis and sometimes terminates in death The writers give arguments in favor of this syndrome being rheumatic activation and speculate as to the exact mechanism of action

MENINGOCOCCAL INFECTION

Antibiotic therapy	Refs 31 32
Bacteriology	Refs 9 11 12 19
Carriers of meningococci	Refs 15 16 19 26
Chemotherapy	Refs 29 30
Clinical	Refs 1 2 3 4 5 13
Epidemics	Refs 8 19
General	Refs 23 25 27
Kernig's sign	Ref 7
Meningococcus bacteremia	Refs 14 20
Meningococcus types	Refs 22 24
Nasopharyngitis	Ref 6
Pathology	Refs 1 2 3 4 5
Serum therapy	Refs 17 18 21 28

MENINGOCOCCAL INFECTION

THE situation as regards meningococcal infection is confused by the great variety of syndromes caused by the meningococcus—epidemic meningitis sporadic meningitis chronic meningococcus sepsis without meningitis acute meningococcal bacteremia without meningitis—the unity of which was not suspected until isolation and identification of the organism were possible We have found no comprehensive modern bibliography of the subject The early literature is largely concerned with the descriptions of epidemics it is thoroughly reviewed and documented by Hirsch (Ref 8) Good general bibliographies are to be found in Foster and Gaskell s book (Ref 25) and in the treatise of C Worster Drought and Alexander Mills Kennedy *Cerebro spinal Fever* (London A & C Black Ltd 1919)

1 VIEUSSEUX Mémoire sur la maladie qui régné à Genêve au printemps de 1805 J méd chir et pharm Paris 11 163 1806

The outbreak at Geneva in 1805 described by Vieusseux is generally taken as the starting point of the modern study of epidemic meningitis As here described one was dealing with a new and violent disease of high mortality featured by sudden prostration or collapse intense headache vomiting at times convulsions rapid feeble pulse and often death in a few hours Most of those who survived several days recovered There is no clear description of petechial spots during life or of stiff neck or opisthotonos At autopsy one saw only a congestion and reddening of the meninges Vieusseux regarded this disease as definite and distinct from other fevers and named it "malignant non contagious cerebral fever" In one family four children were rapidly stricken and all died Tartar emetic was thought to be the best remedy

One would not be absolutely certain of the nature of this disease however were it not for the autopsy reports of Matthey (A Matthey "Recherches sur une maladie particuliere qui a régné à Genève en 1805" J méd chir et pharm Paris 11 243 1806) "The vessels of the meninges were greatly injected A gelatinous humor colored by blood was spread over the entire surface of the brain Over the posterior part of the lobes of the brain and in the interior one saw a yellowish puriform matter without manifest alteration of the cerebral tissue (p 246) "The nervous system seems strongly and directly attacked, for all the symptoms proclaim a brain lesion One sees the bloody engorgement the lymphatic and puriform effusions which explain the inefficiency of the methods which are tried to prevent or dissipate them" (p 249)

2 NORTH E A treatise on a malignant epidemic commonly called spotted fever New York T & F Swords 1811

"It is between four and five years since a new and singular disease which has obtained the name of Spotted Fever first appeared in Medfield in Massachusetts" says North in his Preface (p vii) "Since this time it has prevailed as an epidemic and has proved a most tremendous plague in a considerable number of towns in this state in Massachusetts in Rhode Island in the state of

New York in Vermont and elsewhere sweeping off great numbers of inhabitants No regular treatise calculated to give the public an entire view of this disease has hitherto been published (p vii)

"Whether the spotted fever may be considered as only a variety of cynanche maligna or scarlatina, and be arranged under the order *phlegmasia* or *exanthemata* or whether it ought to be regarded as only a variety of the malignant petechial fever of authors or whether it is a new species of disease to be added to the list of human calamities is yet to be determined" (p 6)

The disease frequently occurred in a very violent form the descriptions resemble those of the bacteremic cases seen in World War I (Ref 14) North mentions in his description "a great surprising sudden loss of strength" "violent pain of the head and many times of the limbs" "syncope," "coma" "mania" "delirium" and "petechiae (pp 10–12) "So frequent indeed was this species of hemorrhage during the first season in which the disease prevailed, that it was considered as one of its most striking characteristics and gave rise to the name *petechial* or *spotted fever* which has been very generally though very improperly applied to the disease In size they [the spots] were various commonly the head of a pin and a six cent bit would mark the two extremes" (p 13) Under Section III (p 15) "On the More Unusual Symptoms of the Fever" it is stated "These are a dilatation and in some a contraction of the pupils of the eyes redness and suffusion of the eyes blindness in some in others double or treble vision a drawing back of the head with a kind of clonic spasm of the muscles of the neck" It seems clear that these cases which correspond more with the present-day sporadic type were relatively less common than the hyperacute (bacteremic?) form As to the cause North is straight eighteenth century "The spotted fever is asthenic in its nature Hence the remote and predisponent causes must be such as debilitate the system" (p 25) There is no suggestion of contagion The long section on treatment is hardly worthy of review North leans heavily on Sydenham and on Huxham

Indeed it would be difficult to be sure of the nature of this disease were there not appended autopsy notes of two cases by Drs L Danielson and E Mann "The second examination was made twelve hours after death on the body of a girl of five years old, of the same family Between the dura and the pia mater was effused a fluid resembling pus" (p 95)

The last half of the book is of special interest it consists of letters from physicians copies of reports of cases and other material dealing with the epidemic

A great problem in the bibliography of cerebrospinal meningitis is the fact that for nearly a century the only recognized form was the epidemic Most of the outbreaks occurred in small towns in garrisons or in other odd places and were described by local doctors with inadequate documentation and usually in obscure or inaccessible medical journals Two examples are *An Inquiry into the Nature and Treatment of the Prevailing Epidemic Called Spotted Fever* by Job Wilson M D (Boston Bradford & Read 1815) and *A History and Description of an Epidemic Fever Commonly Called Spotted Fever* by E Hale Jr M D (Boston Wells & Lilly 1818) Little was added therefore to the knowledge of the disease until the discovery of the causal organism (Ref 9) As to sporadic cases one searches in vain through the older treatises for any

thing definite Without bacteriological study and without lumbar puncture everything was in confusion and whether the case was one of tuberculous meningitis of pyogenic meningitis or of meningococcus meningitis cannot be told In Andral s great collection for example (G Andral *Clinique médicale ou choix d observations recueillies à l'Hôpital de la Charite* [Paris Fortier Masson et Cie 1840] one finds (5 65 17th observation) a report of a case of intense headache at start with vomiting Tendency to sleepiness and immobility Gradual development of coma more and more profound" At autopsy "purulent infiltration of the pia mater at the base of the brain and cerebellum" Whether this was meningococcus meningitis one cannot of course say The various epidemics are however listed in Hirsch (Ref 8)

3 BROUSSAIS C Histoire des méningites cérébro spinales Paris Moquet & Hanquelon 1845

During the years preceding this book there had been numerous and severe out breaks of epidemic meningitis in troops in garrisons all over France The ex *planation of this distribution of the disease now well understood* (Ref 26) was a cause of great perplexity to contemporary observers At any rate the army doctors rendered reports of various local outbreaks and Broussais abstracted and condensed them in his book the special virtue of which is the *numerous careful case reports with autopsy studies* Broussais clearly defined the disease Aside from the excellent descriptions however there is little of value Broussais missed his chance of making a fundamental epidemiological observation "Do the migrations of the various regiments from one part of *France to another account for the propagation of the epidemic?*' he says (p 14) and then adds We shall see that it is impossible to accept this explanation"

4 NIEMEYER F Die epidemische Cerebro spinal Meningitis Berlin August Hirschwald 1865

Niemeyer s monograph was based mostly on personal observations of epidemics in Freiburg Karlsruhe and Rastat Epidemic meningitis had long been thought especially by the French to be a variant of typhus typhoid or some sort of spotted fever Niemeyer took issue with this point of view He insisted that the important symptoms all pertained to intracranial disease and that when convalescence was delayed it depends in unmistakable fashion wholly on the residuals of the meningitis (p 9) This is all confirmed at autopsy where the only significant change is a widespread inflammation of the coverings of the brain and spinal cord (p 10) Furthermore "the changes in the brain cover ings in epidemic meningitis are exactly the same as those found in the sporadic form" (p 10) There are no significant changes in the lymph glands or spleen Niemeyer was however not sure that the disease was an infection and he was willing to admit that atmospheric or telluric causes might be at fault, although he declined to rule out the probability of infection mainly on epidemiological grounds He evidently saw no fulminating hyperacute cases such as those described by the Americans (Ref 5)

The introductory chapter is followed by a detailed description of the pathological anatomy based on fifteen cases Under symptoms are listed severe head ache pains in the neck and back stiffness of neck pains in the extremities

hyperesthesia tetanic cramps in the neck and back muscles convulsions cranial nerve and other palsies psychic disturbances deafness ptosis diplopia pupillary disturbances inflammatory exudate in joints fever etc He concludes this section with the following dicta "All symptoms observed in the course of epidemic cerebrospinal meningitis are clearly accounted for by the purulent inflammation of the pia of the brain and cord" (p 67) Of those affected 69 9 per cent died some of the survivors were deaf or had visual disturbances "The treatment consisted mainly in the energetic use of cold in the form of ice packs to the head leeches behind the ears and calomel internally" (p 71)

The monograph of Mannkopff (*Ueber Meningitis cerebrospinalis epidemica* [Braunschweig Friedrich Vieweg & Sohn 1866]) is noteworthy because of its excellent historical introduction brilliant and detailed clinical account including that of opisthotonus and complete pathological description There is a long philosophical discussion of the etiology and nature of the disease which leads to nothing definite

5 STILLE A On the proper designation of the present epidemic (cerebro spinal meningitis) Am J M Sc 49 121 1865

The extensive recrudescence of epidemic meningitis during the preceding ten years had stimulated an immense amount of discussion as to the nature of the disease and how to classify it The American journals are full of brief articles reporting a few cases usually without autopsy Stillé gives a critical discussion of the whole subject which throws important light on contemporary views He points out that although the disease was first named "spotted fever" even in the early descriptions skin hemorrhages were by no means constantly present he makes a plea for the designation "cerebrospinal meningitis" He then points out the confusion which has arisen with typhus This was evidently due to the occurrence of very acute cases (probably with bacteremia) in which at autopsy when the skull was opened bloody serum gushed out but no actual pus In patients who lived longer however with a less fulminating disease when the pia was opened frank pus was found Stillé did useful work in tracing this spectrum J A Lidell (On epidemic cerebro-spinal meningitis or spotted fever with cases" Am J M Sc 49 17 1865) reports patients who died in a day or two after onset "While sawing off the calvarium and subsequently removing the brain a *large quantity of serum* coloured with blood flowed away W H Draper ("Cerebro-spinal meningitis or spotted fever" Am M Times 9 99 111 1864) described cases he had seen with terrible fatality at Carbondale in the coal regions of Pennsylvania" "Many cases terminated within 12 hours" "In cases which are rapidly fatal the lesion consists simply in an intense engorgement of the sinuses veins and minute vessels of the pia mater with varying amounts of serous subarachnoid and ventricular effusion In more protracted cases the arachnoid is lifted and the surface of the brain obscured by a layer of consistent greenish pus These inflammatory exudations are sometimes confined to the surface of the convolutions sometimes to the base of the brain and in many instances are found in both localities The very high mortality—in some outbreaks nearly 100 per cent—was stressed and the futility of known therapy emphasized In the discussion on etiology Draper stated "The question of contagion in this malady is one of great interest and impor

tance Most authorities agree that it is non contagious This I believe is the conclusion without exception of all observers of the *disease in this country* "

Stille also embodied his ideas in a book *Epidemic Meningitis or Cerebro-spinal Meningitis* (Philadelphia Lindsay & Blakiston 1867)

6 STRUMPELL A Zur Pathologie und pathologischen Anatomie der epidemischen Cerebrospinal Meningitis Deutsches Arch f klin Med 30 500 1882

Important clinical and pathological observations on epidemic meningitis Strumpell quotes a finding of Professor Weigert of "an intensive purulent inflammation of the superior nasopharynx This stimulated the thought that the inflammation in the nasopharynx could furnish a starting point for the investigation of the manner in which the infectious material of epidemic meningitis enters the body especially the areas apparently so shut off as the brain and spinal cord" To this observation many later German writers trace the doctrine of the nasopharynx as portal of entry for the meningococcus

7 KERNIG W Ueber ein wenig bemerktes Meningitis Symptom Berl klin Wchnschr 21 829 1884 (original Vrach St Petersburg 5 427 446 1884)

Kernig describes his well known sign emphasizing its occurrence in epidemic meningitis With the leg flexed at the hip, it is mechanically impossible to extend the knee (*Beugestarre*)

8 HIRSCH A Handbuch der historisch geographischen Pathologie 3 379 2d ed Stuttgart Ferdinand Enke 1886 (English translation by Charles Creighton [London New Sydenham Society 1886] 3 547)

A detailed extremely well documented account of the innumerable epidemics of meningitis cerebro spinalis epidemica " which first described in Geneva in 1805 (Ref 1) occurred with increasing frequency throughout Europe and the United States Even as late as 1886 the disease was thought of as essentially epidemic and Hirsch made no particular mention of sporadic cases He noted that some epidemics were largely confined to children he also pointed out the frequency of epidemics in soldiers in barracks the explanation of which is now of course clear (Ref 26) writing at the beginning of the bacteriological era Hirsch questioned the claims of various bacteriologists (Ref 9) and concluded that the virus was unknown and the disease "not contagious but transportable"

9 WEICHSELBAUM A Ueber die Atiologie der akuten Meningitis cerebro-spinalis Fortschr d Med 5 573 1887

The paper is a model of precise work It was based on post mortem examination of six instances of cerebrospinal meningitis in which Weichselbaum found "an entirely different kind of bacteria than the pneumococci and miscellaneous organisms which were recovered from most sporadic cases of meningitis In the first case there were found in the meningitis exudate and in the ventricular fluid in cover slip preparations a moderate number of cocci usually arranged in pairs with the side toward each other flattened so that each coccus represented a half sphere "They lie either free between the pus cells or inside them where

they are present in considerable numbers and remind one of gonococci" Similar organisms were seen in all the other five cases Weichselbaum was able to cultivate them on agar the growth was fairly delicate and transfer through many generations was difficult They appeared in smears of cultures in pairs tetrads or small clumps Some diplococci were larger than other cells They were stained well with methylene blue and were decolorized by Gram s method They were abundant in sections through the meninges "Because of its characteristic form I will designate this variety of coccus as Diplococcus intracellularis meningitidis" Weichselbaum did not isolate the organism during life this was first done by Heubner (Ref 12) Injections of culture in rather large quantities killed mice guinea pigs rabbits and dogs with various lesions and organisms in the blood stream Weichselbaum suggested the paranasal sinuses or the middle ear as the portal of entry in human cases Interestingly enough Weichselbaum discussed his organisms simply as a cause of one group of meningitis cases he said nothing about having discovered the cause of epidemic meningitis

10 JAEGER H Die Transportmittel gewisser Infectionsstoffe und Vorschlage zur Vernichtung derselben am Krankenbette im Haushalt im Verkehr Deutsche med Wchnschr 20:409 1894

The German ministry of health as early as 1888 (Erlass des kgl Ministers der 2 Cl. Medizinal Angelegenheiten die epidemische Genickstarre [Meningitis cerebrospinalis] betreffend" Veroffentl d k Gsndhtsamte 12 751 1888) laid down rules for the isolation and handling of cases of meningitis based on the conviction that the disease was "communicable and contagious" The disease was made reportable the patients were to be isolated the room and its contents especially handkerchiefs were to be cleaned and disinfected

Jaeger reached the conclusion that the portal of entry for epidemic meningitis was from the nose through the lamina cribrosa to the meninges He therefore examined nasal secretions and in four of five cases found unequivocal" meningococci and from contaminated handkerchiefs he grew the organism in pure culture No meningococci were recovered from the secretions of eight healthy people

This appears to be the first study of meningococcus carriers assuming which seems to us very doubtful that the organisms were meningococci and not *Micrococcus catarrhalis*

11 JAEGER H Zur Atiologie der Meningitis cerebrospinalis epidemica Ztschr f Hyg u Infectionskr 19 351 1895

Weichselbaum described his cocci in sporadic cases of meningitis which were difficult to distinguish from those due to various other organisms especially pneumococcus He was not too emphatic in his claims especially as he was unable to produce the typical disease in animals Otto Leichtenstern ("Ueber Meningitis cerebro spinalis epidemica" Deutsche med Wchnschr 11 391 537 1885) had already found organisms which seemed partly to meet Weichselbaum s description in several cases of meningitis and F Goldschmidt (Zur Aetiologie der Meningitis cerebrospinalis" Centralbl f Bakt 2 649 1887) reported similar confirmatory findings Nonetheless the matter remained in

dispute and little more work was done for a number of years Jaeger studied an outbreak of definite epidemic meningitis and uniformly isolated from the meninges of fatal cases an organism which he regarded as that of Weichselbaum He also found it in sections of tissues and grew it in culture As to animal inoculation he found as did Weichselbaum that subcutaneous injection was totally ineffective He concluded that the meningococcus was a different organism from the pneumococcus of which not everyone had as yet been convinced, and he definitely insisted that the organism of Weichselbaum was the significant finding in epidemic meningitis

However there were several odd points in the findings of Jaeger His organisms did not always decolorize with the Gram stain they sometimes occurred in chains and they could be isolated from dried nasal secretions What was Jaeger actually dealing with? At any rate it remained for H Albrecht and A. Ghon ("Ueber die Aetiologie und pathologische Anatomie der Meningitis cerebrospinalis epidemica " Wien klin Wchnschr 14 984 1901) to give a complete and critical analysis of the literature to date as well as observations of their own and to settle definitely that the cause of epidemic meningitis was the organism of Weichselbaum to explain that it was always Gram negative always fragile and difficult to cultivate and essentially non pathogenic for small animals The findings reported by others of Gram positive forms or organisms resembling pneumococci of readily cultivable organisms were clearly either contaminations or mixed infections This paper is definitive and settled for all time a much vexed question Albrecht and Ghon were also among the first definitely to isolate true meningococci from the nasopharynx

12 HEUBNER O Beobachtungen und Versuche uber den Meningokoccus intracellularis (Weichselbaum Jaeger) Jahrb f Kinderh 43 1 1896

Heubner was the first by means of lumbar puncture to recover Meningococcus from the spinal fluid during life He found typical biscuit shaped" diplococci in pus cells they are also described as like a pair of coffee beans side by side He injected pus containing meningococci intraspinally into goats and produced definite meningitis He grew the organism in pure culture He emphasized the value of spinal puncture in clinical practice in differentiating various forms of meningitis although others such as Lichtheim ("Zur Diagnose der Meningitis Berl klin Wchnschr 32 269 1895) had already dealt with the general subject following Quincke s introduction of lumbar puncture and detailed description of the technique (H Quincke "Ueber Hydrocephalus *Verhandl d Kong f inn Med* [Wiesbaden J F Bergman 1891] 10 321)

13 COUNCILMAN W T MALLORY F B and WRIGHT J H Epidemic cerebro-spinal meningitis and its relation to other forms of meningitis a report of the State Board of Health of Massachusetts Boston Wright & Potter 1898

A comprehensive summary of all phases of the disease supplemented by the authors own early observations in which they confirmed the work of Weichsel baum (Ref 9) There is an excellent historical section

14 OSLER W The arthritis of cerebro-spinal fever Boston M & S J 139 641 1898

In the course of a report of a case of epidemic meningitis with inflammation of the joints and other evidence of sepsis Osler stated that meningococcus was isolated from the blood during life N B Gwyn ("A case of general infection by the Diplococcus intracellularis of Weichselbaum" Bull Johns Hopkins Hosp **10**:112 1899) reported on the bacteriology of the patient Two blood cultures were positive for meningococcus "This is believed to be the first instance recorded in which general infection or septicemia has been demonstrated in this disease" H Cochez and Lemaire ("Relation de l'épidémie de méningite cérébrospinale à Alger et dans les environs" Arch gen de méd **189** 574 1902) were able to grow meningococci from the blood of two patients with meningitis who recovered

H Salomon ("Ueber Meningococcenseptikamie" Berl klin Wchnschr **39**:1045 1902) describes a patient who obviously had a septic fever with purpura (spotted fever) from whose blood meningococcus was recovered Irregular septic fever continued however for several months with repeated isolation of meningococcus from the blood Eventually the patient developed signs of meningitis but recovered. "For two months the meningococcus circulated in the blood while we waited from day to day for meningitis to appear But finally it found its accustomed localization in the intracranial space" This of course is a classical case of chronic meningococcus sepsis However meningococci were soon isolated from the blood in regular cases of meningitis as for example that of A Marcovich ("Meningococcen im kreisenden Blute" Wien klin Wchnschr **19** 1312 1906) who reviewed the early literature

Meanwhile F W Andrewes ("A case of acute meningococcal septicemia" Lancet **1** 1172 1906) described a patient in collapse covered with purpura from whose blood meningococci were grown and in whose blood meningococci were seen *intra vitam* within the leukocytes At autopsy there were hemorrhages everywhere and "both suprarenals were in an intensely hemorrhagic condition dark purple in color swollen and contrasting strongly with the kidneys which were but slightly congested" the case was obviously one of the Waterhouse Friederichsen syndrome [1]

Elser and Huntoon ("Studies on meningitis" J M Research **20** 377 1909) isolated meningococci from the blood in eleven of forty-one cases of meningitis They thought that the organism first gained access to the blood and secondarily localized in the meninges The idea of a preliminary bacteremic stage in epidemic meningitis was strongly emphasized by W W Herrick ("The intravenous serum treatment of epidemic cerebrospinal meningitis Arch Int Med **21** 541 1918) He recognized in an epidemic in an army camp "primary meningococcus sepsis in almost half of the cases before the characteristic selective action on the meninges has been exerted" and he advocated brisk use of serum intravenously as well as intraspinally

[1] Thus Andrewes antedated Waterhouse case by five years (R Waterhouse A case of suprarenal apoplexy" Lancet **1** 577 1911) It is of interest that in the report of the pathologist in the Middlesex Hospital Reports for 1894 there is a pathological report (p 279) of a case with profuse purpura and bilateral hemorrhages into the suprarenal capsules The modern literature is reviewed by L D Weinstein and T H McGavack "The Waterhouse Friederichsen syndrome New England J Med **232**:95 1945

Thus all types of meningococcus infection are illustrated and with any there may be a bacteremia

15 GOODWIN M E and VON SHOLLY A L The frequent occurrence *of meningococci in the nasal cavities of meningitis patients and of those* in direct contact with them J Infect Dis Suppl 2 p 21 1906

The writers *review the earlier papers in which meningococci were claimed to* have been isolated from the nasal sinuses or nasopharynx They conclude that the cultures of only fourteen cases in the literature were studied with sufficient care to warrant their acceptance as true meningococci and they point out that meningococci are easily confused with other Gram negative organisms of the catarrhalis group A Ghon and H Pfeiffer (Der Micrococcus catarrhalis [R Pfeiffer] als Krankheitserreger " Ztschr f klin Med 44 262 1902) gave a detailed discussion of this group point out their frequent occurrence in the upper air passages and discuss the differentiation of them from gonococci and meningococci They emphasize the coarse opaque colonies with ragged edges and the spontaneous agglutinability Although they were not clear that catarrhalis was a member of the normal basic flora of the upper air passages they assigned it a very subordinate role in disease H Jaeger ("Die specifische Agglutination der Meningococcen als Hilfsmittel in ihrer Artbestimmung und zur bacteriologischen Diagnose der epidemischen Genickstarre Ztschr f Hyg u Infectionskr 44 223 1903) prepared immune sera in rabbits with meningococci *and with these was able to recognize specifically other strains* and in general emphasized the value of the procedure *Micrococcus catarrhalis* uniformly failed to agglutinate in these sera Goodwin and von Sholly made nasal cultures with the greatest care Meningococci were isolated from seventeen of thirty seven patients with meningitis when culture was made during the first 2 weeks of the disease whereas meningococci were also isolated in five of forty five healthy persons living in close contact with meningitis patients The organisms *were identified by careful morphological and cultural criteria* and by agglutination tests Goodwin and von Sholly concluded "Meningococci were isolated from nasal mucus of 50 per cent of meningitis patients and from about 10 per cent of the people in closest contact with them They were frequently present in enormous numbers The finding of meningococci in great numbers in the nasal mucus of such a large proportion of the patients and of those caring for them and the absence of meningococci from the nasal mucus of a large number *of normal persons examined would strongly indicate the necessity* of isolating cases of cerebro spinal meningitis " a conclusion reached by the Germans as early as 1888 (Ref 10)

16 KUTSCHER K Ueber Untersuchungen der Nasenrachenhohle gesunder Menschen auf Meningococcen Deutsche med Wchnschr 32:1071 1906

It was already common knowledge that meningococci are frequently found in the nasopharynx of patients with meningitis and of contacts Kutscher made cultures from healthy people who had no known contact with meningitis patients at a time *when no clinical cases existed In fifty six people* he isolated meningococci four times all were agglutinated by specific sera in a titer of

1 500 to 1 1 000 The source of these organisms and the epidemiological implications are discussed Similar findings have since been obtained innumerable times by others

17 JOCHMANN G Versuche zur Serodiagnostik und Serotherapie der epidemischen Genickstarre Deutsche med Wchnschr 32 788 1906

It occurred to Jochmann to try to prepare a potent antimeningococcus serum as a therapeutic agent and also for diagnostic purposes especially to separate true meningococci from other Gram negative cocci He immunized a horse first with dead and then with living culture the serum attained a titer of 1 1 500 The serum specifically agglutinated true meningococci as Jaeger found (Ref 11) Jochmann soon discovered that a considerable number of healthy people in the vicinity of an epidemic harbored meningococci in the nasopharynx as Goodwin and von Sholly had found (Ref 15) *Micrococcus catarrhalis* was not agglutinated Jochmann laid the ghost of widespread claims that there were Gram positive varieties of meningococci by showing that specifically agglutinable strains were always Gram negative He also stressed the fact that his serum was polyvalent. The serum protected mice and guinea pigs against intraperitoneal injection of meningococci Jochmann then treated some forty human cases first with subcutaneous injection and later with intraspinal serum Some of the patients seemed to be helped but Jochmann concluded with the greatest conservatism that the serum at least did no harm These observations opened the long era of serotherapy of epidemic meningitis which did not end until about 1940 Kolle and Wassermann ("Versuche zur Gewinnung und Wertbestimmung eines Meningococcenserum" Deutsche med Wchnschr 32 609 1906) also did important early work on preparing an immune serum

18 FLEXNER, S Concerning a serum therapy for experimental infection with *Diplococcus intracellularis* J Exper Med 9 168 1907

Flexner s interest in meningitis began in connection with the New York epidemic of 1904–5 His first paper (S Flexner "Contributions to the biology of *Diplococcus intracellularis*" J Exper Med 9 105 1907) dealt with the cultural and other biological characteristics of meningococcus Although Annibal Bettencourt and Carlos França ("Ueber die Meningitis cerebrospinalis epidemica und ihren specifischen Erreger" Ztschr f Hyg u Infectionskr 46 463 1904) had failed to produce experimental meningitis in various animals including monkeys Flexner ("Experimental meningitis in monkeys" J Exper Med 9 142 1907) attempted again to produce the disease by lumbar puncture He used huge quantities of bacteria The animals usually died in a few hours or recovered promptly In the fatal cases "meningitis" was found but the organisms tended to die out quickly and it is doubtful whether Flexner produced a condition really analogous to the human disease From this point he went on to treat the experimental disease with immune serum "In summarizing these experiments it may be said that by employment of an homologous antidiplococcus serum several monkeys were saved from death due to experimental infection with Diplococcus intracellularis The monkeys could by simultaneous injection of serum and culture be prevented from developing severe symptoms" However Flexner found "a certain definite protective value

in normal monkey serum also Flexner suggested the possibility of developing more "active antisera" for use in human meningitis

A preliminary report of all the above work appeared in August, 1906 (S Flexner "Experimental cerebrospinal meningitis and its serum treatment, J A M A 47 560 1906)

19 FLUGGE [C] Die Verbreitungsweise und Bekampfung der epidemische Genickstarre Munchen med Wchnschr 54 1059 1907

Flugge summarized concisely the situation as regards distribution of meningococci in relation to the spread of the disease He stated that all patients with epidemic meningitis harbored meningococci in the nasopharynx for the first 5 days after which the organisms usually disappeared rapidly Among contacts about 70 per cent were found to be carriers for 3 weeks or so Since the meningococcus is a delicate organism which does not survive well outside the body the disease must be spread by carriers Flugge had already become interested in meningitis during the German epidemic of 1905 (Die im Hygienischen Institut der Konigl Universitat Breslau wahrend der Genickstarre Epidemie im Jahre 1905 ausgefurten Untersuchungen Klin Jahrb 15 353 1906) This volume also contains many articles by German authorities such as Kolle and Wassermann von Lingelsheim and others which are a mine of information on the details of the disease they are all based on the material studied in this great epidemic

20 LIEBERMEISTER G Ueber Meningococcensepsis Munchen med Wchnschr 55 1978 1908

Liebermeister seems to have been the first to recognize chronic meningococcus spesis as a definite clinical entity apart from epidemic meningitis He reports a classical case with arthralgia prolonged irregular fever positive blood cultures but normal spinal fluid with recovery The voluminous literature on this syndrome is comprehensively reviewed by Dopter (Ref 27 pp 136 ff) Poorly documented cases are however found in earlier reports such as those of E Sacquépée and E Peltier (Meningites cérébrospinales grippales Arch gén de méd 187 537 1901) and of A Cochez and Lemaire (Ref 14) W Dock in 1924 (Intermittent fever of 7 months duration due to meningococcemia J A M A 83 31 1924) was able to collect sixty eight cases from the literature

21 FLEXNER S and JOBLING J W Serum treatment of epidemic cerebro spinal meningitis J Exper Med 10 141 1908

The writers immunized a horse with a mixture of meningococcus strains first given subcutaneously and later intravenously The titer of the serum is not stated Forty seven cases of epidemic meningitis were treated by one to three intraspinal injections of the serum Of the patients 72 3 per cent recovered whereas of untreated cases in the same epidemic about 70 per cent died Flexner and Jobling were conservative but hopeful in their conclusions A little later they reported ("An analysis of 400 cases of epidemic meningitis treated with the anti meningitis serum " J Exper Med 10 690 1908) a large number of cases with a detailed tabulation of results Of these cases only 11–50 per cent died depending upon age as against an over all mortality of at least 75 per cent

in untreated cases They concluded "The antimeningitis serum when used by the subdural method of injection in suitable doses and at proper intervals is capable of reducing the period of illness of preventing in large measure the chronic lesions and types of the infection of bringing about complete restoration to health in all but a very small number of the recovered thus lessening the serious deformity and permanent consequences of meningitis and of greatly diminishing fatalities due to the disease" Meanwhile Harvey Cushing and Frank J Sladen ("Obstructive hydrocephalus following cerebrospinal meningitis intraventricular injection of antimeningitis serum [Flexner]" J Exper Med 10 548 1908) called attention to the possible introduction of serum directly into the ventricles in cases with hydrocephalus and block

But the Germans had not been idle A Wassermann ("Ueber die bisherigen Erfahrungen mit dem Meningococcen Heilserum bei Genickstarrekranken" Deutsche med Wchnschr 33:1585 1907) reported several cases treated by subcutaneous and intraspinal injections of Jochmann s serum with promising results and C Schone (Ueberblick uber die Behandlung von 30 Genickstarre kranken mit Jochmann schen Meningococcenserum " Therap d Gegenwart 48 52 1907) reported on thirty treated cases They achieved results comparable with those of Flexner after intraspinal injection

Flexner later ("The results of the serum treatment in 1 300 cases of epidemic meningitis" J Exper Med 17 553 1913) gave a comprehensive summary of the results of treatment with his serum of cases all over the world The mortality of all treated patients was 30 9 per cent of those treated on the first to third day only 18 1 per cent died At the same time the mortality of untreated cases varied from 70 per cent to 90 per cent Flexner discussed at length the difficulties and complications of serum therapy

With World War I there developed numerous intense epidemics of meningitis especially in the armed forces These epidemics stimulated the studies not only on classification (Ref 24) but on standardization of therapeutic sera taking into account the different strains of meningococcus H L Amoss and M Wollstein ("A method for the rapid preparation of anti meningitis serum" J Exper Med 23 403 1916) led the way in the preparation of potent polyvalent sera with a further report (H L Amoss and P Marsh "Standardization of antimeningitis serum J Exper Med 28 779 1918) dealing largely with criteria for standardization Serum therapy subsequently had a checkered career In the late 1920 s and 1930 s there were severe outbreaks of meningitis which appeared refractory to available sera and had a mortality rate of 70–80 per cent The complexities of this situation in relation to classification of strains is reviewed by Branham (Ref 24) It is interesting to note the way in which things have come full circle so that in 1940 there were again emphasized only two groups of meningococci—Group I responsible for most of the recent epidemics and Group II responsible for most endemic cases and carriers

22 DOPTER C Etude de quelques germes isoles du rhinopharynx voisins du méningocoque (paraméningococcus) Compt rend Soc de biol 67 74 1909

It did not occur to the early writers that there were different types of meningococci distinguishable serologically Dopter isolated organisms from the naso

pharynx which were morphologically and culturally indistinguishable from meningococci and which gave the same reactions in sugars but which differed in certain serological respects These organisms were to be differentiated from the pseudomeningococci of von Lingelsheim which gave different reactions in sugars from true meningococci Dopter felt that his parameningococci had however the same clinical significance as true meningococci Dopter and Pauron (Différenciation des paraméningocoques entre eux par le saturation des agglutinins " Compt rend Soc de biol 77 231 1914) later extended these studies and differentiated various types of parameningococci Up to this time however little or no attention had been paid to differences in strains in clinical work and the sera of Flexner and of Jochmann were prepared from various meningococci selected in empirical and haphazard fashion Dopter led the way in purposeful and intelligent classification of meningococcus strains

23 NETTER A and DEBRÉ R La méningite cérébrospinale Paris Masson et Cie 1911

This classical monograph fully summarizes knowledge of every phase of meningococcus meningitis to date The clinical descriptions are comprehensive and admirable and include such complications as paralysis and visual and auditory troubles The chapter on the nasopharynx as the habitat of the meningococcus is an especially valuable summary The authors offer an explanation for the widely varying number of carriers found by different observers and they conclude that the intensity of the outbreak of meningitis and the carrier rate correspond This was well shown later by Glover (Ref 26)

24 GORDON M H and MURRAY E G Identification of the meningococcus J Roy Army M Corps 24 411 1915

It was thought at first that all meningococci were identical From about 1905 on however numerous workers began to distinguish various races or strains The differentiation was made partly by morphological study partly by fermentation of sugars and partly by serological tests Some of the early papers of importance are those of J A Arkwright ("On variations of the meningococcus and its differentiation from other cocci occurring in the cerebro-spinal fluid J Hyg 7 193 1907 "Varieties of the meningococcus with special reference to a comparison of strains from epidemic and sporadic sources *ibid* 9 104 1909) K Kutscher (Ueber Untersuchungen der Nasenrachenhohle gesunder Menschen auf Meningococcen " Deutsche med Wchnschr 32 1071 1906) William J Elser and Frank M Huntoon ("Studies on meningitis J M Research 20:377 1909) and Dopter (Ref 22) None of these students however arrived at any definitive or uniform classification of meningococci Arthur W M Ellis ("A classification of meningococci based on group agglutination obtained with monovalent immune rabbit serums " Brit M J 2:881 1915) was able to divide meningococci into two groups by agglutination tests and J A Arkwright ("Grouping of strains of meningococcus isolated during the epidemic of cerebrospinal meningitis in 1915 " Brit M J 2:885 1915) came to the same conclusion His two main groups corresponded to Dopter s meningococci and parameningococci (Ref 22)

Gordon and Murray using improved methods for agglutination and absorp-

tion tests were able to distinguish four definite serological types of meningococci among patients in the army Further reports by Gordon appeared (Identification of meningococcus" J Hyg 17:290 1918 *Cerebrospinal Fever* (M Res Council Spec Rep Ser No 50 [London His Majesty s Stationery Office 1920]) This work had important implications in serum therapy and in epidemiological studies Meanwhile similar studies were being made in France by M Nicolle E Debains and C Jouan ("Études sur les méningocoques et les sérums antiméningococciques" Ann Inst Pasteur 32 150 1918) While strains of meningococci have been found which do not fit Gordon s types he brought order into the whole subject and his results have been of practical use For recent comprehensive discussion of the meningococcus see Sara E Branham ("The meningococcus [*Neisseria intracellularis*]" Bact Rev 4 59 1940 "The significance of serological types among meningococci" J A M A 108 692, 1937)

25 FOSTER M and CASKELL J F Cerebro-spinal fever London Cambridge University Press 1916

An excellent survey to date of meningitis based largely on recent military experience The historical section is especially valuable

26 GLOVER J A Observations of the meningococcus carrier rates and their application to the prevention of cerebrospinal fever *in* Cerebrospinal fever p 133 (M Res Council Spec Rep Ser No 50) London His Majesty s Stationery Office 1920

Glover carefully followed the carrier rate in a military installation where there was great crowding Under these conditions with beds only 6 inches apart the carrier rate was found to rise from the normal of 2–4 per cent to the amazing figure of over 70 per cent following which clinical meningitis broke out When the beds were spaced 3 feet apart the outbreak promptly subsided and the carrier rate fell to a low level This phenomenon was repeated several times during periods of crowding Here was final proof that carriers were the source of meningitis and that danger of clinical infection varied with the density of the healthy carrier population A review of this subject is that of K F Maxey ("The relationship of meningococcus carriers to the incidence of cerbrospinal fever Am J M Sc 193 438 1937) Of special interest are the studies of Geoffrey Rake ("Studies on meningococcus infection VI The carrier problem" J Exper Med 59 553 1934) Rake carefully followed a small group of carriers and found that they fell into three categories namely chronic intermittent and transient

27 DOPTER C L'Infection méningococcique Paris J B Baillière et fils 1921

This comprehensive work deals like that of Netter and Debré (Ref 23) with every phase of the subject and leaves little to be added today

28 BLACKFAN K D The treatment of meningococcus meningitis Medicine 1 139 1922

Blackfan reviews the whole history of treatment of meningococcus meningitis including serum therapy

29 BANKS H S Chemotherapy of meningococcal meningitis *Lancet* 2 921 1939

The advent of the sulfonamides sounded the death knell of serum therapy for epidemic meningitis Banks reported 31 cases treated with sulfanilamide without a death and 36 cases treated with M&B 693 with 1 death On the whole patients improved more rapidly with chemotherapy than with serum and the doing away with intraspinal therapy was a great advantage No evidence in favour of auxiliary treatment with serum was obtained" By 1943 Paul B Beeson and Ethel Westerman (Cerebrospinal fever " Brit M J 1 497 1943) were able to discuss sulfonamide therapy in 3 575 cases with an over all fatality rate of 15 94 per cent Serum was also used in some cases among 2 591 cases in whom sulfonamides were used alone the fatality rate was 14 3 per cent Among patients from fifteen to twenty five years old only 5–8 per cent died Similarly A. A. Jubb (Chemotherapy and serotherapy in cerebrospinal [meningococcal] meningitis " Brit M J 1 501 1943) found a death rate of 9 2 per cent in 2 357 cases treated by chemotherapy alone

An earlier note is that of F F Schwentker S Gilman and P H Long ("The treatment of meningococcic meningitis with sulfanilamide " J A M A 108 1407 1937) who treated 11 patients with sulfanilamide subcutaneously and intraspinally with a mortality of 9 per cent

30 MEEHAN J F and MERRILEES C R An outbreak of cerebrospinal meningitis in a foundling hospital the treatment of carriers with M and B 693 M J Australia 2 84 1940

It was known that outbreaks of meningitis ran parallel to the carrier rate but no simple secure method of extirpating meningococci from the nasopharynx had *been discovered The writers treated carrier children after an outbreak of menin*gitis in a foundling hospital with B and M 693" (a sulfonamide) and immediately reduced the carriers from 75 to 3 Similarly R W Fairbrother "Cerebrospinal meningitis the use of sulphonamide derivatives in prophylaxis " Brit M J 2 859 1940) in a very careful study found that adequate dosage with sulphapyridine is a satisfactory method of clearing meningococci from the nasopharyngeal mucosa Finally F S Cheever B B Breese and H C Upham (The treatment of meningococcus carriers with sulfadiazine Ann Int Med 19 602 1943) found that sulfadiazine is effective since all of 161 meningococcus carriers receiving 8 grams of the drug over a period of 72 hours yielded negative cultures on the fourth day

31 MILLER C P and FOSTER A Z Studies on the action of penicillin II Therapeutic action of penicillin on experimental meningococcal infection in mice Proc Soc Exper Biol & Med 56 166 1944

The writers studied the effect of penicillin on experimental meningococcus peritonitis in mice There was a definite curative effect Similarly ("III Bactericidal action of penicillin on meningococcus in vitro " *ibid* p 205) they found that "meningococci are readily killed by penicillin in nutrient broth at 37 "

32 ROSENBERG D H and ARLING P A Penicillin in the treatment of meningitis J A M A 125 1011 1944

The writers reported the first sizable series of meningitis cases treated with peni cillin They gave an intrathecal injection of 10 000 units every day as well as small doses intramuscularly Sixty four of sixty five patients recovered Finland and his associates also in an early report (M Meads W H Harris B A Samper and M Finland "Treatment of meningococcal meningitis with peni cillin" New England J Med 231:509 1944) concluded that penicillin was less satisfactory than sulfonamides and acted more slowly However they had available only small doses of penicillin Recently Lepper and his associates (H H Lepper H F Dowling P F Wehrle N H Blatt H W Spies and M Brown "Meningococcic meningitis treatment with large doses of penicillin compared to treatment with Gantrisin J Lab & Clin Med 40 891 1952) treated meningococcus meningitis with injections of 1 000 000 units of penicillin intramuscularly or intravenously every 2 hours without intrathecal injections Of forty patients only one died These writers conclude that penicillin is just as effective as sulfonamides when large doses are used The earlier studies (E D Dernoff Stanley H F Dowling and L K Sweet "The absorption into and distribution of penicillin in the cerebrospinal fluid" J Clin Investigation 25 87 1946) which showed little if any penicillin in the spinal fluid after parenteral injections were done as it turned out with too small doses of the antibiotic On the other hand Schwemlein and his associates (G T Schwemlein R L Barton T J Bauer L Loewe H N Bundeson and R M Craig Peni cillin in spinal fluid after intravenous administration" J A M A 130 340 1946) found working with syphilitics that significant amounts of penicillin were demonstrated in the spinal fluid after intravenous drip of 10 000 000–25 000 000 units of penicillin in 24 hours

Section 11

GONORRHEA AND GONOCOCCAL INFECTION

Clinical	Refs 1 2 10
Differentiation from syphilis	Refs 1 2
General	Refs 1 2 10
Gonococcal arthritis	Ref 13
Gonococcal endocarditis	Ref 15
Gonococcal infection in females	Refs 9 10 11
Gonococcal lesions of the skin	Ref 14
Gonococcal ophthalmia	Ref 5
Gonococcus	Refs 3 4 6 7 8 10 12
Treatment with antibiotics	Ref 16

Section 11

GONORRHEA AND GONOCOCCAL INFECTION

THE early literature on gonorrhea is concerned largely with the differentiation of the disease from syphilis and the reader is referred to the section on syphilis of this bibliography for pertinent references Innumerable books are available on the subject of gonorrhea of which that by Ernst Finger (*Die Blenorrhoe der Sexualorgane und ihre Complicationen* [Leipzig and Vienna Frantz Deuticke 1888]) is the classical text which ran through many editions and translations Gonorrhea is usually discussed in the general textbooks on venereal and genitourinary diseases and many important articles lie buried in journals on the eye and other special branches Much of course is to be found in the gynecological literature from the time of Bumm (Ref 10) on Among modern texts one should mention the large well documented treatise by Charles C Norris (*Gonorrhea in Women* [Philadelphia and London W B Saunders Co 1913]) and the standard text by P S Pelouze (*Gonorrhea in the Male and Female* [3d ed , Philadelphia and London W B Saunders Co 1939]) which ran through many editions

We have not attempted to follow the bibliography through all the ramifications of the special domains in which the gonococcus may cause disease we have had in mind that this bibliography is primarily for medical students and physicians with general interests

1 BELL Benjamin A treatise on gonorrhea virulenta and lues venerea 2 vols Edinburgh James Watson & Co 1793

Bell was the first clearly to differentiate gonorrhea from syphilis and to insist that it was an independent disease After a general introduction he devotes a full volume to the discussion of the gonorrhea virulenta "Every discharge of matter from the urethra excited by impure coition is termed Gonorrhoea Virulenta" There follow chapters on clinical features of the disease going into minutest details of symptoms and course "The duration of gonorrhoea has always been a matter of much uncertainty" He points out that with simple urethritis "the disease will not commonly endure a fortnight but, wherever the lower parts of the urethra are affected particularly when the prostate gland and other parts about the neck of the bladder are diseased the running in almost every instance proves obstinate (p 67) Bell along with others questioned the value of the medicines in vogue "A low diet mercury and evacuants of different kinds did much harm as we have already observed by inducing such a degree of debility and relaxation as materially affected the constitution" (p 74) The pros and cons of local injections and the use of sounds are discussed The first part of the book ends with an excellent recapitulation "It appears that Gonorrhoea is a local disease proceeding from a specific contagion and not necessarily connected with any other that the discharge of matter which takes place is not the effect of ulceration but proceeds from an inflamed state of the urethra and contiguous parts that the disease is always formidable in proportion to the depth of parts that are affected that in the cure of Gonorrhoea no advantage is derived from mercury or any remedy acting altogether

upon the constitution [in contrast to syphilis] that where the membrane of the urethra is alone affected no remedy proves so successful as astringent injections but that they are never employed but with much risk of doing harm where the inflammation has reached Cowper s glands to the prostate gland or to the bladder that when the bladder is affected opium or hyoscyamus are in like manner to be used to relieve pain" (pp 168 ff) Bell described all sorts of local complications of gonorrhea but was entirely unaware of distant metastases such as arthritis ophthalmia etc The book is nonetheless a masterpiece based as it is on accurate observation of clinical cases

2 RICORD Ph Traité pratique des maladies vénériennes Paris De Just Rouvier & E le Bouvier 1838

The book by Ricord the great French expert on venereal disease deals with both syphilis and gonorrhea although he believed them to be different diseases and proved his point by a great many intradermal inoculations of gonorrheal pus into volunteers without result whereas if the material were syphilitic chancres would be expected to appear Ricord went further than Bell in recognizing some distant complications such as gonococcal ophthalmia "Its development must be attributed to the direct application of the gonorrheal matter to the conjunctiva the first thing to be urged is speed and energy Hesitation and uncertainty are often followed by loss of the eyes one must always insist on applications of silver nitrate" (p 761) The method of application is described in detail Ricord does not however mention the common occurrence of gonococcal arthritis

3 NEISSER Albert Ueber eine der Gonorrhoe eigentumliche Micrococcus form Centralbl f d med Wissensch 17 497 1879

The idea of a bacterial cause of gonorrhea was in the air Thus Lebert (in H von Ziemssen *Handbuch der speciellen Pathologie und Therapie* [Leipzig F C W Vogel 1875] 9 Part II 295) four years before Neisser s discovery said "It is therefore highly probable that gonorrheal pus contains a contagious principle which frankly the microscope and chemical analysis have so far not found. One can suppose that germs develop in the depths of the urethral mucosa Various workers were searching for such a cause at the time In this modest and conservative report Neisser announced the discovery of the gonococcus The organisms were seen in pus from gonococcal urethritis spread thin on slides and stained with methyl violet The intracellular predominance the biscuit shaped pairs of recently divided cocci are well described These bacteria were found in thirty five cases of gonorrhea varying in duration—3 days to 13 weeks—but not in a chronic case of 1 years The gonococcus seemed to be the only organism present Neisser isolated it from nine purulent urethritides in women and from two patients with gonorrheal conjunctivitis Neisser reserved final judgment as to the significance of the organisms pending cultural and inoculation experiments

Neisser s work was soon confirmed in other countries as for example by P Weiss (Thèse de Nancy I ser No 119 [1880]) an abstract of whose work is reported in Ann de dermat et syph (Le microbe du pus blennorhagique") 2 189 1881 Weiss found Neisser s coccus in the gonorrheal discharges of both

men and women and apparently was the first to advise the use of potassium permanganate irrigations 0 25 per 1 000 later much employed O Haab ("Kleinere ophthalmologische Mittheilungen II Parasitare Augenkrankheiten" Cor Bl f schweiz Aerzte 11 79 1881) early confirmed the finding of typical cocci in the discharge of conjunctivitis of the newborn and in gonorrheal ophthalmia He was unable however to grow the organisms in culture

4 LEISTIKOW Ueber Bacterien bei den venerischen Krankheiten Charite Ann 7 750 1880

Leistikow reports confirmation of Neissers work He also undertook culture studies with Loffler and after many failures the "cultures finally throve in a blood serum gelatin at body temperature They tried many inoculation experiments in rabbits dogs rats mice guinea pigs and horses with failure in all to produce disease The results in a monkey were uncertain Leistikow was probably the first to report successful cultivation of the gonococcus Chemotherapy was already under way and he discussed the relative merits of injections of bichloride zinc solutions tannic acid lead acetate silver nitrate and carbolic acid The results were hard to evaluate since gonorrheal discharges ceased of themselves with time

5 CREDE [C] Die Verhutung der Augenentzundung der Neugeborenen Arch f Gynaecol 17 50 1881

Starting from the assumption that conjunctivitis of the newborn was acquired from gonococcal infection of the mother during the babys passage through the birth canal Crede began prophylactic treatment of all newborn babies in the Leipzig clinic He first used various solutions but from 1 June 1880 all eyes without exception were disinfected directly after birth with a single drop of nitrate of silver (1 50) At the same time douching of the mother was discontinued All the children so treated have escaped eye inflammation of even slight grade Mild hyperemia and increased secretion might be present in the first 24 hours, but no harm was ever done to the eyes The main point is in the experience that not disinfection of the vagina but only of the eye achieves the goal" The incidence of conjunctivitis fell in the clinic from 13 6 in 1874 to 0 5 in 1880 In a further communication (*ibid* 18 367 1881) Crede reported 400 new cases in addition to 200 previously recorded The babies eyes were wiped with a cloth dipped in plain water and then "one drop of 2 per cent solution of silver nitrate was instilled No child so treated developed ophthalmia neonatorum in the first 7 days of life" Credé s method was soon generally in use the world over and was relied upon for many years His work was summarized in a book (*Die Verhutung der Augenentzundung der Neugeborenen* [Berlin A Hirschwald 1884])

Penicillin has recently been tried in place of silver nitrate as a prophylactic against gonococcal conjunctivitis The relative merits of the two are analyzed by H C Franklin ("Prophylaxis against ophthalmia neonatorum clinical comparison of penicillin and silver nitrate preliminary report J A M A 134 1230 1947) He leans on the whole toward penicillin although the diminished frequency of maternal gonorrhea makes the problem much less urgent than in Credes day

6 KRAUSE Fedor H Die Micrococcen der Blennorrhoea neonatorum Centralbl f prakt Augenh 6 134 1882

Krause succeeded in growing gonococci from blenorrhea neonatorum using coagulated blood serum as a culture medium He obtained diplococci in pure culture from 12 children Inoculation of the conjunctivae of various small animals was unsuccessful This work was done in Hirschberg s clinic and Hirschberg himself is reported ("Gesellschaft der Charité Aerzte in Berlin 16 Feb 1882" Berl klin Wchnschr 19 500 1882) to have made inoculations with gonorrheal pus into the human eye and invariably to have produced disease although animal inoculation failed At the same meeting early attempts at treatment of gonorrheal urethritis are reported Lewin used bichloride of mercury injections (1 20 000) Guterbock reported that irrigations with water were just as effective and Leistikow found that patients recovered equaly well without any irrigations

7 NEISSER Albert IV Die Micrococcen der Gonorrhoe Deutsche med Wchnschr 8 279 1882

Neisser gives a definitive review of the subject to date He first makes it clear that the gonococcus is a specific organism and again describes its morphological features biscuit shaped diplococci "adherent" to pus cells "Gonococci are absolutely constant in every case of gonorrhea and are not found in any other disease Furthermore the gonococci are the only organisms which are found in gonococcal pus" He now reports success in cultivation of gonococci on meat extract-peptone gelatin "As far as one can ever tell anything by microscopic examination all the doctors who looked at the preparations say that the cultures are pure growths of gonococci (H A Cohnheim Koch Ehrlich) Inoculation of humans with cultures failed however as well as animal inoculations Neisser was unable to find gonococci in pus from gonococcal arthritis and epididymitis but he stressed the occurrence of the germs in ophthalmia

However not everyone accepted the gonococcus as the specific cause of the disease and various conflicting reports in the literature on the specificity and pathogenicity of "gonococci" are reviewed by Bumm (Ref 10)

8 BOCKHART Max Beitrag zur Aetiologie und Pathologie des Harnrohrentrippers Vrtljschr f Dermat u Syph 15:3 1883

Bockhart undertook to inoculate a normal male urethra with a pure culture of gonococci which he received from Dr Fehleisen The subject was a man with advanced dementia paralytica Four days later there was a full blown urethritis with countless gonococci in the secretion A few days later the patient died and at autopsy the sections of the urethra showed gonococci Here then seemed to be undoubted proof that the gonococcus was the pathogenic agent in urethritis Bockhart built up a theory of the pathogenesis of gonorrhea on the basis of lymphatic invasion The distant complications—endocarditis arthritis—he felt come from extension of infection into the blood stream

9 ARNING E Ueber das Vorkommen von Gonococcen bei Bartolinitis Vrtljschr f Dermat u Syph 15 371 1883

Arning found gonococci regularly in acute and chronic inflammation of Bartholin s glands in women At about the same time E Bumm ("Beitrag zur Kentniss

der Gonorrhoe der weiblichen Genitalien" Arch f Gynaecol 23 328 1884) the gynecologist made a systemic study of gonococcal infection in women and pointed out the "most frequent site of gonorrhea is the mucosa of the cervix uteri" But to confuse matters Bumm found organisms resembling gonococci in the genitals of women where the possibility of gonorrhea was absolutely excluded These cocci were biscuit shaped diplo forms and were readily cultivable on artificial media where they grew out as milk white plaques which produced no lesion when inoculated on mucous membranes One suspects that these bacteria were members of the *N catarrhalis* group They were also found in ulcerative processes in the mouth and in sputum

10 BUMM Ernst Der Micro Organismus der gonorrhoischen Schleimhaut Erkrankungen Gonococcus Neisser" Wiesbaden J F Bergmann 1885

This little book which is a definite landmark in the subject opens with a critical review to date of the literature on the gonococcus There follows a description of the morphology and staining and a discussion of numerous biscuit shaped diplococci other than gonococci—a lemon yellow diplococcus not pathogenic a milk white diplococcus not pathogenic a yellow white diplococcus pathogenic a pink diplococcus not pathogenic All these need to be differentiated from the gonococcus Bumm lists the "pathological secretions in which the gonococci occur male and female urethritis bladder and kidney periurethral abscesses knee joint conjunctiva rectum body and cervix of the uterus Bartholin s glands Bumm summarizes the position of the gonococcus in diagnosis "The presence of Neisser s gonococcus in the secretions proves the infectious origin of the disease of the mucous membrane and conversely gonococcus free secretion has no virulent characteristics" Bumm gradually assembled a considerable amount of pathological tissue from which he was able to build up the histological appearance of gonococcal infection day by day until the thirty third day—a fundamental piece of work He next summarizes the literature on attempts to cultivate the gonococcus on artificial media and describes his own successful work pointing out the difficulties and the ease with which confusion could arise with other diplococci which were readily cultivable He feels that Neisser did not grow genuine gonococci whereas Fehleisen probably and Leistikow definitely did Bumm inoculated the urethra of a healthy woman and produced gonococcal urethritis once more proving the pathogenic specificity of the organism

Bumm s summary brings out very well the difficulties of the subject at the time principally the confusion of gonococci with other diplococci in smear and in culture He also speculated about distant lesions as to whether they were due to spread of gonococci through the body or whether they were sympathetic" or due to an absorbed toxin—questions which vexed everyone at the time However his monograph was definitive to date and left relatively little of importance untouched

11 FRAENKEL, Eugen Bericht uber eine bei Kindern beobachtete Endemie infectioser Colpitis Virchows Arch f path Anat 99 251 1885

The syndrome of vulvovaginitis in little girls was recognized in the early part of the nineteenth century as pointed out in the excellent reviews of the literature of Cahen Broch ("Die Urogenital Blenorrhoe der kleinen Madchen" Jahrb f

Kinderh 31:369 1892) and of A Epstein ("Ueber Vulvovaginitis gonorrhoica bei kleinen Madchen" Arch f Dermat u Syph 23:3 1891) The occurrence in little girls the relative immunity of boys and of girls after menstruation started the usual non venereal nature of the spread of the disease the association of the child with a mother who had gonorrhea the occurrence in institutions where many children were in close contact and where a common bathtub and towels were used were all stressed R Pott (Die specifische Vulvo-Vaginitis im Kindesalter und ihre Behandlung, Jahrb f Kinderh 19:71 1883) was among the first to insist that this disease was "the expression of a specific communicable disease of the mucous membrane" and to point out how widespread it was in the general population The above writers give detailed descriptions of the findings and clinical course of the condition and the chronic character and great resistance to disinfectants and astringents were noted by everyone Fraenkel however was the first to establish definitively the gonococcus as cause of the disease He studied the discharges and "the finding was very striking since there was success in demonstrating in every preparation the presence of a micro-organism which differed in no respect from the gonococcus of Neisser"

The large modern literature on the subject is reviewed by R A Benson and A Steer ("Vaginitis of children" Am J Dis Child 53 806 1937) Recently A Cohn A Steer and E L Adler (Gonococcal vaginitis" Ven Dis Inform 21 208 1940) could only prove that 23 3 per cent of cases of juvenile vaginitis were definitely gonococcal and they placed more emphasis than most observers on actual sexual contact However both sulfanilamide and sulfapyridine produced rapid cures Like all other manifestations of the gonococcus vaginitis responds promptly to penicillin (B G Clarke and H H Eisenberg "Gonococcic vaginitis in children treated with single injection of penicillin in beeswax and peanut oil report of twenty cases" Am J Dis Child 74 707 1947)

12 WERTHEIM Ernst. Reinzuchtung des Gonococcus Neisser mittels des Plattenverfahrens Deutsche med Wchnschr 17 1351 1891

Wertheim modified previous cultural procedures so that he readily grew gonococci in plates of serum peptone agar He inoculated the urethras of five men with general paresis and in every case produced typical gonorrhea from which the gonococci were again recovered Wertheim considered that his experiments gave final and indisputable proof that the coccus of Neisser was actually the cause of gonorrhea The observation has often been repeated by various observers

Modern work on the complexity of suitable media for growth of the gonococcus is summarized in the article by J F Mahoney and J D Thayer *in* R J Dubos *Bacterial and Mycotic Infections of Man* (2d ed Philadelphia J B Lippincott Co 1952) page 565 As methods have been improved cultures have been found to have as valuable a place in diagnosis as direct smears (see C M Carpenter *et al* "Evaluation of twelve media for the isolation of the gonococcus" Am J Syph 33 164 1949 and J D Thayer J H Schubert and M A Bucca The evaluation of culture mediums for the routine isolation of the gonococcus J Ven Dis Inform 28 37 1947)

13 HOCK Heinrich Ein Beitrag zur Arthritis blennorrhoica Wien klin Wchnschr 6 736 1893

The concept of gonococcal arthritis seems to have grown slowly so that Brandes of Copenhagen ("Du rhumatisme blenorrhagique" Arch gén de méd 4 257 1854) could open his paper with the question "Does blenorrhagic rheumatism really exist?" Apparently some of the alleged cases were only instances of vague aches and pains or they may have been some other variety of arthritis Brandes reports several cases of gonorrhea associated with arthritis but, as there was no bacteriological confirmation they are difficult to interpret He points out that this form of arthritis is much more common in men than in women and that it often accompanies ophthalmia The complication of cardiac lesions is rare very rare but it is not impossible The knee is the joint most often affected although the trouble migrates from joint to joint Ankyloses of large joints rarely occur G Bucker (*Ueber Polyarthritis gonorrhoica* [Inaug diss Berlin 1880]) reviews the whole subject and reports two cases in which pus was withdrawn from joints but apparently no search was made for Neisser s coccus

A step forward was made by L M Petrone ("Sulla natura parasitaria dell artrite blenorrhagica" Riv clin di Bologna 3 94 1883 which is abstracted in Centralbl f Chir 10 586 1883) who found in smears from the joint exudate of two cases of urethritis and arthritis bacteria which corresponded in every respect with Neisser s organisms One does not know what to make of the statement that the cocci were seen also in the blood presumably in smears In the following year F Kammerer ("Ueber gonorrhoische Gelenkentzündung" Centralbl f Chir 11 49 1884) also saw typical gonococci in the exudate of an inflamed knee joint but neither of these observers brought the final proof of the existence of gonococcal infection of joints by cultivating the organism

Hock seems to have been the first to isolate gonococci from a joint which was the seat of acute arthritis Interestingly enough his patient was a baby with gonococcal ophthalmia he reviews a number of other instances of arthritis following gonococcal ophthalmitis in which organisms were seen in smears but were not cultured Neisser ("Ueber die Züchtung der Gonococcen bei einen Fall von Arthritis gonorrhoica Deutsche med Wchnschr 20 160 1894) shortly after reported culture from the knee and finger of an adult with gonococcal arthritis and finally Bordoni Uffreduzzi ("Ueber die Localization des Gonococcus im inneren des Organismus [durch den Gonococcus herforgerufene Pleuritis und Arthritis]" Deutsche med Wchnschr 20 484 1894) produced urethritis in a volunteer with a culture of gonococcus obtained from a case of arthritis That the gonococcus could spread in the body and produce distant lesions now seemed understandable

C S Keefer and W W Spink ("Gonococcic arthritis pathogenesis mechanism of recovery and treatment" J A M A 109 1448 1937) give a definitive modern discussion of the subject up to the antibiotic era They point out certain associated lesions such as metastatic catarrhal conjunctivitis iridocyclitis and keratodermia blenorrhagicum and the occasional occurrence of bacteremia even without endocardial involvement In another paper ("Latent gonorrhoea as a cause of acute polyarticular arthritis" J A M A 109:325 1937) they emphasize the fact that gonococcal arthritis may occur when the primary urethral infection gave no overt manifestations

The modern therapy of gonococcal arthritis begins with the use of artificial

fever the results of which are summarized by R M Stecher and W M Solomon ("The treatment of gonorrhoeal arthritis with artificial fever" Am J M Sc 192 497 1936) Of a series of fifty cases twenty-six were relieved of all joint symptoms eleven received benefit, while thirteen were not helped Because of the strenuous and complicated character of fever therapy it was soon replaced by chemotherapy when the sulfonamides were found effective C. S Keefer and L. A Rantz (Sulphanilamide in the treatment of gonococcal arthritis" Am. J M Sc. 197:168 1939) were the first to report a careful study They found that in adequate dosage the drug diffused into the synovial fluid which was sterilized in several days The "results are encouraging and all patients with gonococcal arthritis should be treated intensively with the drug" J H Linner ("Suppurative myositis and purulent arthritis complicating acute gonorrhoea" J.A.M.A., 123 757 1943) was the first to report a case treated with penicillin N Spitzer and O Steinbrocker ("The treatment of gonococcal arthritis with penicillin" Am J.M Sc. 218 138 1949) later reviewed the subject and found that among twenty-eight cases "23 were regarded as cured or greatly improved 5 as failures"

14 VIDAL, Émile Éruption généralisée et symétrique de croutes cornees avec chute des ongles d origine blenorrhagique coincidante avec une polyarthrite de meme nature Recédive à la suite d une nouvelle blenor rhagie deux ans après la guérison de la premiere maladie Ann de dermat et syph 4 3 1893

Vidal appears to have been the first to describe thoroughly the skin lesions of gonorrhea and to note their association with arthritis "The recurrence of these lesions, the pathogenesis of which was in doubt in 1890 shows that they are a direct manifestation of the gonorrheal infection just as arthritis is" J G Downing ("Keratoderma blenorrhagicum" J.A.M.A., 102 829 1934) reviews the literature with a case report of his own as do W W Spink and C. S Keefer ("The renal and dermatologic complications of gonococcal infection" New England. J Med. 217 241 1937) The first American case was that of F E Simpson ("Keratodermie blenorrhagique" J.A.M.A., 59 607 1912) whose paper is especially useful because it contains abstracts of the previously reported cases A W French S Schwartz, and O Steinbrocker ("Penicillin in the treatment of keratosis blenorrhagica with polyarthritis" Arch Int. Med. 79 239 1947) treated three cases with penicillin with brilliant cures in two of them

15 THAYER William Sidney and BLUMER George Ulcerative endocarditis due to the gonococcus gonorrhoeal septicemia Bull Johns Hopkins Hosp 7 57 1896

J Marty ("De l endocardite blenorrhagique" Arch gen. de med., 28 660 1876) gives brief excerpts of several cases from the literature and reports two of his own in which an attack of gonorrhea was followed by arthritis and signs of endocarditis He gives an excellent discussion of the whole subject, but, as his own patients did not die and as there was no bacteriological confirmation it remains uncertain whether these were really cases of gonococcal endocarditis Previously Lacassagne ("Des complications cardiaques de la blenorrhagie"

Arch gen de méd 19 15 1872) reviewed the subject of serous membrane involvement with gonorrhea and he reports a number of cases of pericarditis including one of his own which he regards as of gonococcal origin Thayer and Blumer review the reports of several recent cases of endocarditis in which gonococci were presumably seen in smears from the heart valves at autopsy but the final proof of cultures was not obtained Their own patient ran the typical course of ulcerative endocarditis At autopsy there were vegetations of the mitral valve containing what were morphologically typical gonococci The organisms were recovered in blood culture during life and were grown from the valve after death Here then was the first proved case of gonococcal sepsis with ulcerative endocarditis Modern statistics on this lesion may be found in Thayer's monograph *Studies on bacterial (infective) endocarditis*" Johns Hopkins Hosp Rep Vol 22 Fasc I 1926 W S Thayer and J W Lazear (A second case of gonococcal septicemia and ulcerative endocarditis with observations upon the cardiac complications of gonorrhoea J Exper Med 4 81 1899) soon reported a second case of gonococcal bacteremia with extensive vegetations on the tricuspid valve and multiple purulent lesions They review the literature and point out that there are five cases (including their own two) in which *the gonococcal nature of the infection is definitely proved* But they go further and emphasize that the gonococcus may on occasion act exactly like the pyogenic cocci and produce a general sepsis with multiple purulent lesions and bacteremia Grave myocardial changes necrosis purulent infiltration embolic abscesses are common in severe gonococcal septicaemias

the diagnosis may in some cases be made during life by cultures taken from the circulating blood The article is a classic Thayer later (On the cardiac complications of gonorrhoea Bull Johns Hopkins Hosp 33 361 1922) again wrote on the subject

One wonders what effect modern drugs and antibiotics would have on this *serious disease* E S Orgain and M A Poston (*Gonococcal endocarditis* with recovery after sulfapyridine" New England J Med 221 167 1939) report a case with recovery after treatment with sulfapyridine and P H Futcher and V C Scott ("Four cases of gonococcal endocarditis treated with sulfanilamide with recovery of one Bull Johns Hopkins Hosp 65 377 1939) using strict *criteria had one recovery after transfusion and sulfanilamide* whereas three other patients treated with sulfanilamide died Further to complicate the interpretation spontaneous recovery or recovery following transfusion alone has been reported fairly often Futcher and Scott review the literature on "spontaneous recovery from gonococcal endocarditis and bacteremia

16 HERRELL W E COOK E N and THOMPSON L Use of penicillin in sulfonamide resistant gonorrheal infections J A M A 122 289 1943

E P Abraham *et al* (Further observations on penicillin Lancet 2 177 1941) had shown that the gonococcus was highly sensitive to penicillin in the test tube Herrell and his associates confirmed this observation and seem to have been the first to use the material in clinical gonorrhea Because of *very limited amounts of penicillin available they treated only sulfonamide resistant* cases "The complete absence of toxicity following the intravenous administration of pyrogen free penicillin the lack of any discomfort to the patient and

the rather rapid disappearance of clinical symptoms have been observed in three cases of sulfonamide resistant gonorrheal infection In all the cases reported in addition to the clinical response noted negative bacterial cultures were obtained some time between seventeen and forty eight hours after the institution of penicillin therapy" A little later J F Mahoney C Ferguson M Bucholtz, and C J Van Slyke ("The use of penicillin sodium in the treat ment of sulfonamide resistant gonorrhea in men Am J Syph 27:525 1943) reported cure of seventy two of seventy five cases of gonorrhea with a total of only 160 000 units of penicillin over a treatment period of 45 hours Since then the supremacy of penicillin in treatment of gonorrhea has been universally confirmed as for example by T H Sternberg and T B Turner ("The treat ment of sulfonamide resistant gonorrhea with penicillin sodium" J A M A 126:157 1944) C P Miller W W Scott and V Moeller (Studies on the action of penicillin I The rapidity of its therapeutic effect on gonococcic ure thritis" J A M A 125:607 1944) found that intramuscular doses of 50 000–100 000 units of penicillin were followed by rapid disappearance of gonococci from cases of urethritis

Section 12

TUBERCULOSIS

Allergy	Refs 51 59 60
Bacteriology	Refs 28 29 32 37 65 66
Bovine	Refs 23 31 45 52
Childhood type	Refs 25 53 56
Clinical features	Refs 1 2 4 5 8 10 17 19
Etiology	Refs 13 15 16 18 20 23 28 31 32 37 44 52 56 58 61
Immunity and resistance	*Refs 36 38 39 40 41* 43 49 51 56 57 58 59 60 61 67 70
Mass surveys	Ref 61
Pathology	Refs 1 2 4 5 13 17 19 21 34 47
Prevention	Refs 9 37 38 39 40 41 44 57 61
Reinfection	Refs 56 58 61
Skin test	Ref 49

(*Continued on following page*)

Surgery	Refs 30 35 42 54
Transmission	Refs 16 18 19 20 22 23 24 26 28 31 32 37 44 56 58
Treatment	Refs 8 19
Treatment–antibiotics	Refs 62 63 64 68 69
Treatment–hygienic	Refs 11 15 27 55
Treatment–pneumothorax	Refs 3 30
Tuberculin	Refs 39 41 46 48 50
Tuberculosis choroidal	Ref 14
Tuberculosis of kidney	Ref 12
Tuberculosis of meninges	Ref 7
Tuberculosis of spine	Ref 6
Tuberculosis of tonsil	Ref 33
Vaccination	Refs 38 57

Section 12

TUBERCULOSIS

IT HAS been our purpose in this bibliography beginning with the nineteenth century to list all the fundamental contributions to a subject so far this has not seemed an insuperable task With tuberculosis however we confess that our courage has been daunted The vast size of the subject the limitless literature and the innumerable facets have we fear made it impossible to include every major contribution especially those of recent years Perhaps this list should be called "high spots" of tuberculosis rather than a "bibliography" On the other hand we have been heartened by the fact that no such effort seems to have been made previously by the conviction that anyone perusing this chapter will gain a good general conception of the history of tuberculosis and the significance of the disease and finally by the knowledge that the references which we have listed give ready access to further pursuit of the literature

It is difficult for the modern student to realize how vague and rudimentary the knowledge of tuberculosis was at the beginning of the nineteenth century Medicine was just emerging from the Galenic doctrine of humors little was known about morbid anatomy and cellular pathology was still in the future Jaundice dropsy and fever were thought of as diseases in themselves rather than as symptoms and so too those people who wasted away with cough blood spitting and "hectic" fever were loosely spoken of as "consumptives" As more and more autopsies were done especially by the early nineteenth-century French clinician pathologists certain distinct appearances were noted in the lungs of many of those who died It was the clearer definition of the clinical features of consumption by physical examination along with formulation of the various anatomical changes found at autopsy that dispelled some of the obscurity which was not lifted until the transmission experiments of Villemin (Refs 18 22) and the discovery of the bacillus by Koch (Ref 28)

The modern student must also realize that a hundred and fifty years ago what we now think of as early tuberculosis was completely unrecognized Doctors dealt largely with advanced disease and such disease was highly prevalent As the young Brontes dropped off one by one of consumption this was accepted more or less as a matter of course Anne consented to see a physician only on the day of her death Laennec himself was consumptive and Keats hardly more than a boy died in the arms of his friend Joseph Severn a wraith racked by cough and hemorrhage

As in the case of so many diseases it is almost impossible to decide who among all those who wrote on consumption and on tubercle first really sensed their true relationship Matthew Baillie and G L Bayle certainly deserve mention before one goes on to Laennec who towers above all contemporaries in the field

We know of no really complete bibliography of tuberculosis The little *Historical Chronology of Tuberculosis* is of great value but unfortunately contains few actual references The modern literature on infection and immunity is well covered in the Bibliography of Rich s monumental work (Ref 67) The

masterful Essays on Tuberculosis by Allen Krause which he buried in the *Journal of Outdoor Life* for the years 1918–23 should be reprinted Flicks large volume is full of generous quotations but again gives no systematic bibliography Pinners book is especially useful because the numerous references are each followed by a critical abstract Finally Dubos readable volume lists a number of the most comprehensive reviews as well as many books ancillary to the main subject but of great interest

Burke Richard M *A Historical Chronology of Tuberculosis* Springfield Charles C Thomas 1938

Flick Lawrence F *Development of Our Knowledge of Tuberculosis* Philadelphia 1925

Pinner Max *Pulmonary Tuberculosis in the Adult* Springfield Charles C Thomas 1925

Dubos Rene and Dubos Jean *The White Plague* Boston Little Brown & Co 1952

1 BAILLIE Matthew The morbid anatomy of some of the most important parts of the human body 3d ed London J Johnson 1807

This must be regarded as one of the great medical books of the nineteenth century in a day when writing about disease was usually fanciful and speculative we find here clear and precise descriptions based on objective observation Not only was Baillie a great physician in his day but he was not dated

'The object of this work is to explain more minutely than has hitherto been done the changes in structure arising from morbid action in the human body "The human mind is prone to form opinions upon every subject which is presented to it but from a natural indolence is frequently averse to inquire into the circumstances which can alone form a sufficient ground for them This is the most general cause of false opinions which have not only pervaded medicine but almost every other branch of knowledge When however the mind shall be obliged to observe facts which can not be reconciled with such opinions it will be evident that the opinions are ill founded and they will be laid aside We grant it does not always happen that men are induced to give up their opinions or even to think them wrong upon observing facts which do not agree with them but surely it is the best means of producing this effect and whatever change may be wrought on the individuals themselves the world will be convinced who have fewer prejudices to combat These remarks from the Preface strike the keynote to the descriptions which follow

As regards tuberculosis what Baillie had to say seems sound as far as it goes But both the anatomical description and the clinical remarks are brief and obviously inadequate Under the heading of "Tubercles" we read There is no morbid appearance so common in the lungs as that of tubercles These consist of rounded firm white bodies interspersed through their substance" They are at first very small being not larger than the heads of very small pins and in this case are frequently accumulated in small clusters The smaller tubercles of a cluster probably grow together and form one large tubercle" "When cut into they are found to consist of a white smooth substance having a firm texture and often contain in part a thick curdy pus "When several tubercles of considerable size are grown together so as to form a pretty large tubercu

lated mass pus is very generally found upon cutting into it" "When tubercles are converted into abscesses phthisis pulmonalis is produced one of the most destructive diseases in this island" In cutting into the lungs a considerable portion of their structure sometimes appears to be changed into a whitish soft matter somewhat intermediate between a solid and a fluid like a scrofulous gland just beginning to suppurate"

The clinical side is described as follows "When tubercles are forming in the lungs but have not advanced to suppuration they are attended with a slight cough with occasional difficulty of breathing and a pulse somewhat accelerated These are symptoms which commonly usher in phthisis pulmonalis and are frequently overlooked " "When the tubercles have begun to suppurate and abscesses to be formed then there is an expectoration of a thick pus which is occasionally tinged with blood emaciation debility and hectic fever"

Baillie is sternly objective There is no hint as to his views (perhaps he had none) on cause contagion etc

2 BAYLE G L. Recherches sur la phthisie pulmonaire Paris Gabon 1810

By this time the concept of tubercle as a small "tumor" was well established Now there began an era of lively discussion Are all tubercles the same? What is the significance of the lesions often seen with tubercle such as diffuse infiltrations caseation and abscess? Are tubercles in other organs the same process as in the lung? What clinical symptoms go with various lesions? How does tubercle arise? Is it contagious? These and many other questions were soon under violent debate often with special pleading Bayle was prominent in these discussions and often reported on the subject to the society of the Paris school of medicine Laennec frequently refers to his work However Bayle s treatise of 428 closely printed pages is rather disappointing beginning with his definition of the *essential character* of phthisis Pulmonary phthisis should include *every lesion of the lung which left to itself produces a progressive disorganization of this viscus in the train of which ulceration supervenes and finally death*" (p 5) This is a bad start since this definition obviously includes abscess tumor mycoses etc Nor is one encouraged by reading (p 18) that there are six forms of phthisis—tuberculous granular melanotic ulcerous calculous and cancerous

However under the heading of "Tuberculous Phthisis" there are descriptions of what was doubtless tuberculosis although there is no clear recognition of evolution from tubercle to cavity On the whole Bayle s discussions seem confused, even though there are bits of good description They are usually impaired furthermore by extraneous and inconsequential material One wonders whether Bayle s reputation as a phthisiologist is not largely due to his recognition by Laennec although actually Laennec usually refers to him only to disagree Certainly Bayle s book is not so satisfying as Baillie s brief discourse on tubercle

3 CARSON James Essays physiological and practical pp 61–65 Liverpool Printed by F B Wright 1822

One would hardly mention Carson s recommendation of artificial pneumothorax in pulmonary tuberculosis if it were only a casual suggestion But in these essays he reports careful physiological experiments in which he recog

masterful Essays on Tuberculosis" by Allen Krause which he buried in the *Journal of Outdoor Life* for the years 1918–23 should be reprinted Flick's large volume is full of generous quotations but again gives no systematic bibliography Pinner's book is especially useful because the numerous references are each followed by a critical abstract Finally Dubos readable volume lists a number of the most comprehensive reviews as well as many books ancillary to the main subject but of great interest

Burke Richard M *A Historical Chronology of Tuberculosis* Springfield Charles C Thomas 1938

Flick Lawrence F *Development of Our Knowledge of Tuberculosis* Philadelphia 1925

Pinner Max *Pulmonary Tuberculosis in the Adult* Springfield Charles C Thomas 1925

Dubos René and Dubos Jean *The White Plague* Boston Little Brown & Co 1952

1 BAILLIE Matthew The morbid anatomy of some of the most important parts of the human body 3d ed London J Johnson 1807

This must be regarded as one of the great medical books of the nineteenth century in a day when writing about disease was usually fanciful and speculative we find here clear and precise descriptions based on objective observation Not only was Baillie a great physician in his day but he was not "dated"

The object of this work is to explain more minutely than has hitherto been done the changes in structure arising from morbid action in the human body The human mind is prone to form opinions upon every subject which is presented to it but from a natural indolence is frequently averse to inquire into the circumstances which can alone form a sufficient ground for them This is the most general cause of false opinions which have not only pervaded medicine but almost every other branch of knowledge When however the mind shall be obliged to observe facts which can not be reconciled with such opinions it will be evident that the opinions are ill founded and they will be laid aside We grant it does not always happen that men are induced to give up their opinions or even to think them wrong upon observing facts which do not agree with them but surely it is the best means of producing this effect and whatever change may be wrought on the individuals themselves the world will be convinced who have fewer prejudices to combat These remarks from the Preface strike the keynote to the descriptions which follow

As regards tuberculosis what Baillie had to say seems sound as far as it goes But both the anatomical description and the clinical remarks are brief and obviously inadequate Under the heading of Tubercles" we read "There is no morbid appearance so common in the lungs as that of tubercles These consist of rounded firm white bodies interspersed through their substance" They are at first very small being not larger than the heads of very small pins and in this case are frequently accumulated in small clusters The smaller tubercles of a cluster probably grow together and form one large tubercle" "When cut into they are found to consist of a white smooth substance having a firm texture and often contain in part a thick curdy pus When several tubercles of considerable size are grown together so as to form a pretty large tubercu

points towards the bottom must be the youngest of all the tubercles There must have been successive *crops* of tubercles or eruptions as he styled them He recognized too that the changes that were often to be found in the bowels the kidneys the bones the glands and other organs of consumptives were tuberculous"

Laennec did not believe that tuberculosis was infectious or communicable but he insisted that the disease was curable especially in the early stages contrary to general opinion at the time but like most he felt that there was no doubt about hereditary predisposition

No student of tuberculosis can afford not to read the original text the masterly exposition of a genius or at least a good translation

5 LOUIS P Ch A Recherches anatomico-pathologiques sur la phthisie Paris Gabon et Cie 1825

Louis was one of the greatest of the French clinician pathologists of the early nineteenth century He had a remarkable capacity for precise unbiased observation and for clear and beautifully written descriptions Louis opens his Preface by exclaiming that one may be surprised to "see appear new researches on phthisis following the recent work of Bayle and M Laennec" (p vi) Louis did add however a great deal He paid special attention to tubercle in other organs than the lungs "These researches" says the report to the Royal Academy of Medicine which precedes the actual text (p 5) "made with minute care have led M Louis to a very important conclusion None of the 358 subjects which he has autopsied has shown tubercles in any other organ unless they were also present in the lung"

Louis confined his observations to tuberculosis and it seems to us that he gave a clear over all picture of the disease hardly surpassed by Laennec As a matter of fact Louis s book appeared in the year preceding Laennec s second (and best) edition

The book is in two parts "Pathologic Anatomy" and Symptoms and Treatment" The first part deals systematically with the lesions illustrated by careful autopsy reports many of which might well have come from a modern department of pathology In the second part the clinical features are admirably detailed The various stages of the disease—early late etc—are discussed as well as the symptoms of involvement of organs other than the lung

Louis like everyone in his day had only vague ideas of etiology and seems to have taken no definite position about the spread of the disease at any rate there is no suggestion that he thought tuberculosis communicable

The section on treatment is brief When the symptoms were mild he ordered an infusion of lichen a gummy potion and often a small dose of syrup of diacode to calm the cough and procure a little sleep Leeches bleeding blisters and all sorts of medicines were tried in more severe cases and for hemoptysis

As with Laennec any serious student of tuberculosis must carefully study Louis s book one cannot do justice to it in a few words The report of the committee of the academy (p 16) concludes We think that the Academy specially charged to give a good direction to medical studies should encourage the number always very small of those who instead of following the crowd with speculative discussions devote their lives to gathering observations at the

nized the problems of lung elasticity and intrathoracic pressure relations and he studied artificial pneumothorax in animals "It is my recollection to have read of cases of consumption having been cured by the chest being deeply wounded in battle I am now disposed to place in those histories a degree of credit which I confess I did not formerly yield to them The cure depended upon the reduction of the diseased and wounded lung to a state of collapse The operation which I have ventured to suggest should be purposely performed was in these cases roughly indeed made by accident" He recognized that sudden total collapse might be risky "To obviate these dangers the plain and simple means are to reduce the lung to a state of collapse *by degrees only This might be accomplished, by admitting a small quantity of* air into the cavity of the chest at one time and allowing an interval to exist between the successive admissions "It has long been my opinion that if ever this disease (consumption) is to be cured and it is an event of which I am by no means disposed to despair it must be accomplished by mechanical means or in other words by a surgical operation

Carson thought in terms of open pneumothorax and it was not until years later that closed pneumothorax was developed by Forlanini and others The history of the whole subject is set forth in Otto Mistal *Die Vorlaufer von Forlanini in der Pneumothorax Therapie* (Zurich and Leipzig O Fussli 1929) and by L R Davidson M Furhman and V J Bella "The precursors of Forlanini and Murphy" Am Rev Tuberc **40** 292 1939

4 LAENNEC R T H Traité de l auscultation médiate et des maladies des poumons et du cœur Seconde édition entierement refondue Paris J S Chaude *1826*

The second and most complete edition of Laennec s classic appeared in 1826 the year of his death from consumption The section on tuberculosis occupies pages 532–728 in Volume 1 It is impossible in a bibliography of this sort to do adequate justice to Laennec s epoch making work by brief quotations so packed with new views are these pages A brief summary however would include the following using the new methods of physical diagnosis especially the stethoscope Laennec recognized and classified the pulmonary lesions of consumptives during life He clearly showed the relation of anatomical tubercle to the clinical disease and defined the various types of lesion As Krause has admirably summarized it ("Essays on tuberculosis J Outdoor Life **15** 6 1918) "He recognized that the yellow tubercles were a later stage of the small round gray tubercles that as the small tubercles grew and developed their boundaries joined to form more extensive areas or diffuse changes that these latter in turn could undergo degeneration disintegration and liquefaction so that in time cavities might result. In other words all these varied and apparently dissimilar changes were different phases of the same process—tubercle There was only one disease —consumption though its symptomatic manifestations might be as kaleidoscopic as the entire range of medicine itself Consumption was a unity and tubercle was a unity and consumption and tubercle were indissolubly linked And as he gazed at such lungs Laennec saw even more The cavity at the top he taught must be the oldest process the yellow diffuse cheesy patches lower down must have started later the numerous minute grayish and yellowish

colored plates in which the author took great pride but which seem crude to the modern eye

Under "Treatment" there are advised for various indications bleeding spirits of turpentine elixir of vitriol common salt opium sugar of lead cupping blisters issues rest gum water farinaceous food infusion of sage prussic acid digitalis iodine uva ursi sarsaparilla fumigation from boiling tar and potash (in truth I have seen it act like a charm" p 135) There are prescriptions about diet clothing exercise and climate ("a mixture of sea and land air is unfavorable to delicate lungs" p 145) "Nothing seems to exert a more decidedly favorable influence on the lungs than unmixed sea air" (p 150) "Although consumption makes its chief havoc among the poor and the miserable we often see it invade without distinction the abodes of temperance of refinement and of luxury and number among its victims the young the accomplished and the beautiful! The reason is obvious The midnight application of the student the imprudence of dress so common among fashionable females and the various excesses which too often form a part of the recreation of the wealthy produce those same liabilities to consumption which though from different causes are entailed upon the indigent and the miserable" (p 164)

9 CLARK James A treatise on pulmonary consumption London 1835 (American edition from which we quote [Philadelphia Carey Lea & Blanchard 1835])

The comments made on Morton s treatise apply equally to Clark s The latter s claim to distinction was his great emphasis on prevention He was a pioneer in public health. In the Dedication of his book to Leopold I king of the Belgians he says It is only by convincing the public of the comparative futility of all attempts to cure consumption and of the signal efficacy of proper measures directed to prevent it that physicians can ever hope to produce those beneficial results in improving public health and in preserving and prolonging human life which it is the distinguishing privilege of their profession to aim at" (p iii) And from the Preface (p vii) "My great aim has been to point out the nature and causes of the constitutional affection in which tuberculous diseases have their origins and on those to found rules for prevention and treatment" But since Clark had no idea that the disease was infectious or communicable but thought that it "has its origin in a morbid state of the constitution" his praiseworthy ideas could not be put into very successful practice although some of them happen to coincide with more rational procedures Clark made useful statistical studies in trying to get at the cause of tuberculosis He pointed out the pulmonary changes which occurred in workers in dusty trades such as miners and stonemasons and he undoubtedly described silicosis and silicotuberculosis But shoemakers tailors and weavers were thought prone to tuberculosis because of their sedentary employment and strained posture whereas seamen butchers and tanners were considered more or less exempt because of the "free and regular exercise in the open air which they enjoy" There is an interesting chapter on tuberculous disease in animals As to cause almost every conceivable circumstance is mentioned except contagion "The view which I take of tuberculous cachexia without which in my opinion tuberculous disease of the lungs can not occur leads me entirely to disbelieve that consumption can be com

bedside to seeking after death to trace the disorders which have preceded and led to them and to deduce from the combination of these facts inescapable conclusions

It should be emphasized that in this entire era the pathogenesis of anatomical tubercle was completely obscure Many writers regarded it as the result of inflammation" although this process itself was only vaguely defined or as an outgrowth of bronchitis or peripneumonia" All this was very indefinite Others regarded tubercle as a local secretion

6 DELPECH J L Orthomorphie[1] 1 240 Paris Gabon 1828

Delpech seems to have been the first clearly to distinguish tuberculosis from other diseases of the spine He points out that tubercles of vertebrae are the cause of the mal vertébral de Pott" "The state of science is such on this point that it is appropriate today to call this disease tuberculosis of the vertebrae this will be the first time it has received a characteristic name There follows an excellent and comprehensive description of the clinical features and pathology amplified by an atlas of fine illustrations Every orthopedist should be familiar with Delpech s book

7 [PAPAVOINE Louis Nicolas] Observations d arachnitis tuberculeuse par M Papavoine interne des hopitaux J hebd de méd 6 113 1830

An excellent and comprehensive clinical and pathological description of two cases of tuberculous meningitis which may be contrasted a century later with the recent report of Lorber on 549 cases (John Lorber The results of treatment of 549 cases of tuberculous meningitis Am Rev Tuberc 69 13 1954)

8 MORTON Samuel George Illustrations of pulmonary consumption its anatomical characters causes symptoms and treatment Philadelphia Key & Biddle 1834

After the pioneer work of Laennec and of Louis there was little fundamental advance in the subject until Villemin thirty years later Most of the contemporary accounts leaned heavily on the great French authorities At best there were amplifications but no one questioned their basic anatomical findings As to etiology contagion and treatment on the other hand there were bitter disputes and strong arguments about trivial points Therapy had advanced but little beyond medieval empiricism much of it was supported by the fallacious anecdotal method Clinical descriptions dealt almost entirely with the advanced disease with wasting cavitation and hectic fever

Morton s treatise should be noted because it is the first book printed in the United States on tuberculosis and because it illustrates very well the above points "My attention was particularly directed to diseases of the lungs by an attendance on the clinical lectures of the celebrated Laennec who with astonishing acuteness of mind and personal urbanity combined the faculty of imparting a portion of his enthusiasm to all who heard him" (p viii) There is a systematic discussion of lesions and of symptoms illustrated by autopsies and by

[1] Full title *L Orthomorphie par rapport à l'espèce humaine ou recherches anatomico pathologiques sur les causes les moyens de prévenir ceux de guérir les principales difformités et sur les véritables fondemens de l'art appelé orthopédique*

13 VIRCHOW Rud Ueber die Verschiedenheit von Phthise und Tuberculose Verhandl d phys med Gesellsch Wurzburg 3:98 1852

Virchow criticized Laennec s views on tuberculosis and insisted on the non identity of phthisis and tuberculosis To the modern student this seven page discussion seems almost absurd since it is based on anatomical criteria which are meaningless now Virchow did perhaps rightly claim that Laennec centered too much attention on the lungs when tuberculosis was actually a widespread disease but on the whole he confused and held back the subject until Villemin s transmission experiments But when one realizes that even today the various gross appearances of tuberculosis cancer and pyogenic and mycotic infections may be confused and that cavitation may take place in tumor as well as in tuberculosis or pyogenic infection Virchow s position does not seem too illogical It was perhaps because Virchow knew so much that he became confused

Virchow s doctrine may be briefly summarized somewhat as follows The diffuse caseating pulmonary lesions described by Laennec may develop out of all sorts of lung disease such as ordinary pneumonia or bronchitis When these diffuse lesions occur the patient has the clinical features of consumption Discrete small tubercles are something else and have nothing to do with consumption although they are harmful and the combination of tubercle and consumption is considered especially serious Or as Niemeyer said "The worst thing that can happen to a consumptive is that he become tuberculous"

14 JAEGER Eduard Ueber Choroidealtuberkel Oesterreich Ztschr f prakt Heilk 1:9 1855

This seems to be the first description of choroidal tubercles Although brief everything worthwhile is said The tubercles are described as seen with the ophthalmoscope and at autopsy It is pointed out that they cause no eye symptoms unless in the macular region The author raises the question of whether tuberculosis cannot be diagnosed earlier by recognition of choroidal tubercles than by other methods

Choroidal tubercles must have been much more common in the days of extensive disseminated tuberculosis than at present

15 BREHMER Herrmann Die chronische Lungenschwindsucht Berlin Th Chr Fr Enslin 1857

The key to Brehmer s character is found on the title page of this book, where he says of it "For unprejudiced doctors and critically thinking laymen" and below Motto In the natural sciences the authority of thousands cannot contradict the simple reasoning of a single man

Was Brehmer a quack or only an enthusiast? In this his first book—a mass of pseudo-physiology and superficial rationalism—he may well scoff at the ridiculous ideas of others but this is hardly a defense of his own The abnormally small heart the weakness of its walls are the one and only cause of acquired tuberculosis and consumption" (p 69) On an elaboration of this thesis he built up his cosmos of therapy—life in the mountains with a special course of feeding and of baths He developed one after another the great sanatoria of Gorbersdorf in the Silesian Riesengebirge" Under his system at a time when consumption was thought incurable many of the tuberculous undoubtedly got well he em

municated by contagion (p 182) Obviously then Clark s rules for prevention had no rational basis He urged that members of families "predisposed to tuberculosis" should not marry because their tuberculous constitution was thought hereditary "By placing the predisposed child in the most favorable circumstances as regards those agents which exert a constant influence on the health such as food air exercise etc we may improve the constitution so as to overcome the hereditary predisposition" (p 207) As to actual therapy Clark was no better than Morton the use of emetics in tuberculosis for example fills nine pages (pp 255–64)

10 TROUSSEAU A and BELLOC H Traite pratique de la phthisie laryngee, etc Paris J B Baillière 1837

Although this book has been referred to as if it dealt entirely with tuberculosis of the larynx the authors used phthisis in the general sense common at that time of a wasting disease Actually only a few pages are devoted to laryngeal tuberculosis mainly in the form of case reports These are done however, in masterly fashion and there can be no doubt that the authors were dealing with advanced laryngeal lesions in association with pulmonary tuberculosis These are well illustrated by plates and are clearly distinguished from cancerous syphilitic, and other forms of laryngeal phthisis This monograph of nearly five hundred pages is done in Trousseau s best style and was "crowned by the academy It brought order where confusion had existed although Louis and others had had something to say on the subject

11 BODINGTON George An essay on the treatment and cure of pulmonary consumption on principles natural rational and successful London Longman Orme Brown Greene & Longmans 1840 also reprinted by the New Sydenham Society in Selected essays and monographs (1891)

This essay is a landmark in the history of the treatment of pulmonary consumption The writer was the first to discredit completely the irrational and useless current methods of treatment bleeding tartar emetic digitalis demulcents blisters leeches and plasters Although Bodington s basis for therapy was actually meaningless as we see it today ("the main ground of the treatment has been to preserve or restore to a normal condition the functions of the nervous filaments interwoven with the substance of the lungs and exercising influence over the capillary system and other parts of the organization) what he proposed agreed essentially with the best modern management up to the time of surgery and antibiotics His plan consisted of quiet residence in the country with plenty of fresh air easing of stress moderate exercise an abundant simple diet and sedatives There are case reports of patients with advanced disease who recovered under this program which antedated Brehmer Dettweiler and Trudeau by a good many years

12 RAYER P Traite des maladies des reins etc 3 618 Paris J B Baillière 1841

Rayer seems to have been the first to present a comprehensive description of the various forms of tuberculosis of the kidney ureter and bladder In fifty seven pages the literature is reviewed the pathology is described and there are excellent case reports and illustrations

13 VIRCHOW Rud Ueber die Verschiedenheit von Phthise und Tuberculose Verhandl d phys med Gesellsch Wurzburg 3:98 1852

Virchow criticized Laennec s views on tuberculosis and insisted on the non identity of phthisis and tuberculosis To the modern student this seven page discussion seems almost absurd since it is based on anatomical criteria which are meaningless now Virchow did perhaps rightly claim that Laennec centered too much attention on the lungs when tuberculosis was actually a widespread disease but on the whole he confused and held back the subject until Villemin s transmission experiments But when one realizes that even today the various gross appearances of tuberculosis cancer and pyogenic and mycotic infections may be confused and that cavitation may take place in tumor as well as in tuberculosis or pyogenic infection Virchow s position does not seem too illogical It was perhaps because Virchow knew so much that he became confused

Virchow s doctrine may be briefly summarized somewhat as follows The diffuse caseating pulmonary lesions described by Laennec may develop out of all sorts of lung disease such as ordinary pneumonia or bronchitis When these diffuse lesions occur the patient has the clinical features of consumption Discrete small tubercles are something else and have nothing to do with consumption although they are harmful and the combination of tubercle and consumption is considered especially serious Or as Niemeyer said "The worst thing that can happen to a consumptive is that he become tuberculous"

14 JAEGER Eduard Ueber Choroidealtuberkel Oesterreich Ztschr f prakt Heilk 1:9 1855

This seems to be the first description of choroidal tubercles Although brief everything worthwhile is said The tubercles are described as seen with the ophthalmoscope and at autopsy It is pointed out that they cause no eye symptoms unless in the macular region The author raises the question of whether tuberculosis cannot be diagnosed earlier by recognition of choroidal tubercles than by other methods

Choroidal tubercles must have been much more common in the days of extensive disseminated tuberculosis than at present

15 BREHMER Herrmann Die chronische Lungenschwindsucht Berlin Th Chr Fr Enslin 1857

The key to Brehmer s character is found on the title page of this book where he says of it For unprejudiced doctors and critically thinking laymen" and below "Motto In the natural sciences the authority of thousands cannot contradict the simple reasoning of a single man"

Was Brehmer a quack or only an enthusiast? In this his first book—a mass of pseudo-physiology and superficial rationalism—he may well scoff at the ridiculous ideas of others but this is hardly a defense of his own "The abnormally small heart the weakness of its walls are the one and only cause of acquired tuberculosis and consumption" (p 69) On an elaboration of this thesis he built up his cosmos of therapy—life in the mountains with a special course of feeding and of baths He developed one after another the great sanatoria of Gorbersdorf in the Silesian "Riesengebirge" Under his system at a time when consumption was thought incurable many of the tuberculous undoubtedly got well he em

phasized starting treatment in early cases and some of his patients probably did not have tuberculosis at all Like most of the successful sanatorium men his follower Dettweiler Trudeau at Saranac and in modern times others such as Peers of Colfax and Pottenger of Monrovia he had a tremendous personality Morale faith and hope no doubt played their part in Brehmer s cures but we can find no shred of rational basis in what he did other than the elimination of the old harmful nostrums and depleting measures together with a certain amount of rest although this was not carried out as a purposeful measure Brehmer reported some of his cases from time to time ("Zur Therapie der chronische Tuberculose" Deutsche Klin 17:126 1865) and later wrote another book (*Die Therapie der chronischen Lungenschwindsucht* [Wiesbaden J F Bergmann 1887]) as enthusiastic as polemical and with as little sound basis as his earlier essay Like most men of this sort, he was a fighter with a chip on his shoulder and, despite his uncompromising vigor somewhat on the defensive Much has been written about Brehmer mostly with admiration or even reverence although he was at first scoffed at Now his work is often approached as one might a shrine Certainly many of his patients worshiped him His influence has dominated all subsequent sanatoria and open air methods of treatment (see for example Hugh M Kinghorn "Herrmann Brehmer" Tr Am Climat & Clin A 37:193 1921 Vincent Y Bowditch, "Visits to Brehmer s and Dettweiler s sanatoria" J Outdoor Life 16 65 1919)

16 BUHL [Ludwig] Bericht über 280 Leichenoffnungen Ztschr f rat. Med 8:1 1857

Buhl seems to have been the first to emphasize the fact that miliary tuberculosis resulted by blood borne dissemination from an earlier focus "Miliary tuberculosis appears therefore, to be a specific infectious disease and has the same relation to its portals of entry as pyemia with its multiple abscesses has to a primary focus of suppuration or acute miliary carcinosis has to its primary growth" (p 50) In a later paper ("Psoasabscess mit nachgefolgter Miliartuberculose" Wien med Wchnschr 9 195 1859) by Buhl s associates it is stated that "a special poison the tuberculous element enters the blood from a caseous or suppurative focus and sets up at innumerable points" military tubercules These were advanced views which implied an infectious agent, but the matter was still controversial when Buhl s book was published years later (Ludwig Buhl, *Lungenentzundung Tuberculose und Schwindsucht* [Munich Rudolph Oldenbourg 1872] see pp 112–14) It was Weigert, however who first described the ulceration of tuberculous foci into the thoracic duct and vena cava ("Die anatomischen Wege des Tuberkelgiftes" Wien med Presse 24 1373 1883)

17 VILLEMIN J A *Du tubercle au point de vue de son siège de son évolution et de sa nature* Paris J B Baillière et fils 1862

With the great school of French clinician pathologists of the early nineteenth century there arose a vast literature on the morbid anatomy of disease Following Laennec, innumerable discussions on "tubercle" appeared most of which are unreadable and meaningless to the modern student The great Virchow had confused not clarified, the issue (Ref 13) Villemin, later to do epoch making work on transmission (Ref 18) gives no indication in this little monograph

written only three years earlier that he considered tubercle communicable But in this systematic anatomical study he clearly points out that caseation and calcification are later stages of what begins as tubercle He did not regard the process as a specific disease but thought the sequence might occur in any inflammation He noted however the frequency of tubercle in the lungs and lymph nodes

We cannot reprint Villemin s thirty five general conclusions which occupy four pages of his book A few however are as follows (II) "Later one sees that these tuberculiform processes have a common property that of transforming themselves after a while into a material of peculiar consistency which one compares to cheese and to which one applies the epithet *caseous* (V) "From this point on *caseous matter* and *tubercle* become synonymous" (XVI) "The tuberculous process passes thus through fatty caseous and calcific stages but this property is not specific (to tuberculosis) it is general to all organic matter" (XXXI) "The intensity of the cause which produces tubercle does not affirm itself by the size of the morbid lesions but by their multiplication and their generalization through the whole economy"

One senses in the record of these dark gropings some confused glimpses of the truth but no further real progress could be made until communicability of a specific lesion was proved That was Villemin s great contribution Up to this point he seems far behind Laennec

18 VILLEMIN J A Cause et nature de la tuberculose Bull Acad de méd Paris **31**:211 1865

From long study of the clinical and pathological features of tuberculosis Villemin became convinced that "tuberculosis is the result of a specific causal agent in other words a virus This agent should be found in the morbid products which it has produced by direct action on the normal elements of the affected tissues Introduced into a susceptible organism it should then reproduce itself and at the same time the disease of which it is the determining cause" He then presented proof that this was true by a series of precise experiments This work was so epoch making that we shall quote in detail from one of the many observations

First series of experiments On March 6 we took two young rabbits about 3 weeks old In one of these rabbits we made a little wound behind the ear and inserted two small fragments of tubercle and a little purulent liquid taken from a cavity in the lung of a tuberculous man dead 23 hours On March 30 and April 4 we repeated the inoculations June 20 we sacrificed the two rabbits We found in the inoculated one [that] the lungs are filled with large tuberculous masses formed by the agglomeration of several granulations The control rabbit *showed absolutely no tubercle*"

Villemin s conclusions from many similar experiments were "Tuberculosis is a specific affection Its cause resides in an inoculable agent Inoculation from man to rabbit works very well Tuberculosis belongs then to the class of virulent diseases and should be placed in the nosological framework side by side with syphilis but even closer to glanders"

In a second paper (Cause et nature de la tuberculose Bull Acad de méd Paris 32 152 1866) Villemin continued and elaborated his first experiments He pointed out first that true tuberculosis was pretty much confined to man

monkey cattle and rabbit he believed that so-called tubercles in other animals were due to parasites He now made systematic studies on inoculation from man to rabbit cow to rabbit rabbit to rabbit man to guinea pig (*cochon d'Inde*) These were all successful but inoculations from man to dog, cat sheep and fowl failed to produce definite tuberculosis

Villemin s work was so novel and so important if true that the academy appointed a commission to appraise it critically In a long report ("Rapport sur deux communications de M Villemin ayant pour titre Cause et nature de la tuberculose—*Commissaires* MM Louis Grisolle H Bouley et G Colin *rapporteur*" Bull Acad de méd Paris 32 897 1867) Colin reported that the commission had confirmed and verified Villemin s work and concluded "Consequently it [the academy] has the honor to propose

"1 That the author of the two lectures on tuberculization be thanked

"2 That he be invited to pursue the studies which he has so well begun

"3 And finally to recommend his work or at least the unpublished part of it to your committee for publication

Thus Villemin was promptly vindicated and the current textbook legend that he fought for years for recognition by the Paris medical authorities is obviously incorrect

In the same session of the academy at which Villemin s second report was presented Lebert (Quelques expériences sur la transmission par inoculation des tubercles par M le professeur H Lebert à Breslau " p 119) reported his experiences on the transmission of tubercle which he clearly reproduced in guinea pigs and rabbits inoculated with human material Lebert made the valuable observation that while the lesions varied in the donor they were quite similar in the recipient animals Lebert stated that his experiments had been going on for years no mention was made of Villemin s report of the year before Nor was there mention of any experimental work in Lebert s large and excellent treatise on tuberculosis (H Lebert *Traité pratique des maladies scrofuleuses et tuberculeuses* [Paris J B Baillière 1849])

19 VILLEMIN J A Etudes sur la tuberculose Paris J B Baillière et fils 1868

In this monograph of over six hundred pages Villemin elaborated all his work on tuberculosis—clinical pathological and experimental These experiments prove the great analogy between tuberculosis and the best understood virulent *diseases* The evolution of tubercle depends on the point of inoculation the time which elapses between the moment of this inoculation and tuberculous eruptions in various organs the initial tubercle developing at the point of insertion of the virulent material becomes the source of the generalization of the disease just as in syphilis

One can readily understand the immense importance of Villemin s work.

20 [CHAUVEAU A] Tuberculose expérimentalement produite par l inges tion de viande tuberculeuse par M le professeur Chauveau (résumé d une lecture faite à l Académie de Medecine) Gaz méd Lyon 20 550 1868

The transmission experiments of Villemin were not yet generally accepted Strong support for the communicability of tuberculosis was given by the obser

vations of Chauveau a veterinarian who fed tuberculous material to young healthy calves They soon became ill and when they were sacrificed on the fifty second day there were found the most beautiful lesions of generalized tuberculosis with marked predominance in the intestine and mesentery" The lungs also were studded with tubercles Chauveau raised the question then whether the portal of entry for tuberculosis might not be by way of the digestive tract as well as the lungs which had previously been regarded as paramount He immediately saw and emphasized the public health aspects and the dangers "against which it is important to take sanitary police measures" Chauveau s work raised a storm of protest in some quarters mainly because of the danger ous implications to man

The early literature on the whole question of contagion of tuberculosis by in gestion as well as by inhalation is vividly analyzed by Krause (Essays on tuber culosis" J Outdoor Life 15 295 1918)

21 LANGHANS Th Ueber Riesenzellen mit wandstandigen Kernen in Tuberkeln und die fibrose Form des Tuberkels Virchows Arch f path Anat 42 382 1868

It is difficult to decide from the vast literature who deserves credit for the first adequate histological description of tubercle Certain it is that the earlier ac counts such as those of G Cluge (*Atlas der pathologischen Anatomie* [Jena F Manke 1850]) are entirely inadequate Langhans at any rate first clearly emphasized the characteristic giant cell of tubercle but his pictures are really quite deficient and reflect the primitive histological methods of the day

22 [VILLEMIN Jean Antoine] De la propagation de la phthisie par le docteur Villemin professeur au Val-de Grâce mémoire lu à l Académie de Médecine dans sa séance du 13 avril 1869 Gaz hebd de méd 6 260 1869

Here Villemin reports fundamentally new experiments He now made subcuta neous injections of fresh sputum into rabbits and also injections of dried pow dered sputum Typical lesions were produced in all the animals He also showed that, while fresh dried sputum caused lesions it lost its "inoculability" if the sputum stood for several days before desiccation or if the sputum was dried too long before injection Infectious material fed or introduced by stomach tube yielded typical lesions but injections of sweat from tuberculous patients failed to transmit the disease "Tubercle and expectorated material from the tubercu lous behave like virulent substances they produce tuberculosis by inoculation and by absorption through the natural routes (digestive respiratory) But what one must never forget in the production of every transmissible disease is that there are two factors the morbid germ on the one hand and the more or less great susceptibility of the organism It is because one pays no attention to the second that one goes wrong" and blames on anger fear fatigue etc "near ly every disease such as typhoid typhus plague cholera as well as scurvy pellagra glanders phthisis cancer etc"

23 GERLACH A C Ueber die Impfbarkeit der Tuberculose und der Perlsucht bei Thieren sowie uber die Uebertragbarkeit der letzteren durch Futterung Virchows Arch f path Anat 51 290 1870

The work of Gerlach is a milestone in the understanding of the transmission of tuberculosis and of the significance of bovine tuberculosis Gerlach first set about to confirm Villemin s experiments which he did by inoculating into animals material from tuberculous cows He then turned his attention to milk Milk from an old tuberculous cow whose disease (*Perlsucht*) was confirmed at autopsy was fed to five animals representing four different species All developed typical tuberculous lesions The mesenteric nodes were invariably much enlarged and seemed to represent the oldest lesion although there were changes in the lungs and elsewhere Gerlach quite justly concluded that he had produced tubercle and that "Perlsucht" *i e* bovine tuberculosis was probably the same disease as human tuberculosis He promptly saw the public health implications—that milk of doubtful origin was no longer safe as a "wet nurse" for children nor was it safe to eat flesh even if cooked, of cattle who might be tuberculous He pointed the way to the extirpation of bovine tuberculosis The revolutionary character of these observations is clear when one realizes that at the time "Perlsucht" of cattle had been completely exonerated as a source of human tuberculosis

The correctness of Gerlach s claims was not immediately recognized nor did everyone accept the tremendous public health implications A bitter controversy was waged for many years before everyone was convinced by the finding of tubercle bacilli in the udders of cows The work of T Smith (Ref 45) on the different reactions of animals to human and bovine tubercle bacilli helped greatly to clear up some of the misunderstandings It is of interest that a great deal of this work was done by veterinarians

The whole subject is skilfully analyzed by A Krause ("Essays on tuberculosis" J Outdoor Life 15:295 327 1918)

24 ARMANINI Luciano Sulla specificità e virulenza della sostanze caseose e tuberculose ricerche sperimentali Movimento med-chir 4 233 1872

Although Villemin s great work on transmission of tuberculosis now seems unassailable it was by no means generally accepted at the time A huge controversial literature arose and many able workers thought that they could explain Villemin s findings on other grounds than the transfer of a living virus To Armanini seems to go the credit for the use of a method later employed by Cohnheim (Ref 26) which went far to prove transmissibility Armanini scarified the corneas of guinea pigs with a needle dipped in tuberculous material At the end of ten days no lesion was apparent But on the twentieth day small gray nodules which were undoubtedly tubercles appeared although Armanini himself was conservative in interpreting the findings This was only a part of Armanini s extensive transmission experiments The paper is comprehensive and gives full credit to previous workers in other countries It deserves to be reprinted in English

25 [PARROT Joseph Marie Jules] Abstract of report at the meeting of October 28 1876 Compt rend Soc de biol 28 308 1876

The definition of the primary pulmonary lesion of childhood tuberculosis is usually attributed to Ghon (Ref 53) but he himself disclaimed credit for prior

ity and pointed out that Parrot as early as 1876 had fully recognized and de scribed the focus in the lung and the associated hilar adenopathy Parrot s brief communication is very much to the point He showed that in children (one to seven years old) every tuberculous hilar node is associated with a pulmonary focus which usually appears the older of the two Previous students had in the main believed that hilar nodes occurred without any lung lesion or that the two might be quite independent Parrot pointed out the need for meticulous search through the lung if the primary focus was to be found "At this time of life there is no affection of the lung which is not reflected in the bronchial nodes they are as it were the mirror of the lungs and vice versa There is no bronchial node adenopathy which does not have a pulmonary origin"

The subject is extensively developed in Georges Kuss s book (*De l'hérédité parasitaire de la tuberculose humaine* [Paris 1898]) Kuss reviews the older literature and adds many observations of his own although the book deals primarily with the question of hereditary tuberculosis

26 [COHNHEIM J and SALOMONSEN] Reports on experimental tuber culosis Jahresb d Schles Gesellsch f vaterl Kult 55 222 1877

Cohnheim was apparently unaware of Armanini s work (Ref 24) on experi mental ocular tuberculosis The method may however have been suggested to him by the work of W Goldzieher ("Ueber Implantationen in die vordere Augenkammer" Arch f exper Path u Pharmakol 2 387 1874) although Goldzieher s experiments dealt with foreign bodies poisons etc and not with infectious material In this brief report Cohnheim and Salomonsen described the introduction of minute particles of tuberculous material into the anterior chamber of rabbits As in Armanini s work the eyes were perfectly clear for a few days but after about 2 weeks there "suddenly appeared in the tissue of the iris one or more tiny light gray nodules" They concluded "(1) that inocula tion tuberculosis develops independently of traumatic inflammation and (2) that inoculation tuberculosis has an incubation period in the rabbit of something over 3 weeks

This work sponsored by the great German pathologist went far toward con vincing everyone of the transmissibility of tuberculosis Salomonsen reported the experiments in great detail ("Om Impodning af Tuberculose sarligt Kammens iris" Nord med ark 11 1 1879) and Cohnheim himself sum marized them in his little monograph *Die Tuberculose vom Standpunkte der Infectionslehre* (Leipzig 1880) K Schuchardt finally ("Die Impftuberculose des Auges und ihr Zusammenhang mit der allgemeinen Impftuberculose" Vir chows Arch f path Anat 88 28 1882) reviewed the whole subject and ana lyzed the relation of experimental ocular tuberculosis to generalized experi mental lesions

27 DETTWEILER P Die Behandlung der Lungenschwindsucht in geschlossenen Heilanstalten mit besonderer Beziehung auf Falkenstein i/T Berlin G Reimer 1880

Dettweiler patient and pupil of Brehmer (Ref 15) is credited with being the first systematically to use complete rest in the treatment of pulmonary tubercu losis He had no idea however that healing of the tuberculous process could be

directly promoted by rest but prescribed it for incidental difficulties such as "heart weaknesses" or "severe anemia" If these were marked he had the patient recline all day in the open air on a comfortable couch Breathing exercises and mountain climbing are discussed only in relation to their effect on the heart. This treatise of 129 pages somewhat ponderously written also stresses plenty of food and goes into innumerable other facets of the cure as practiced at Falkenstein The influence of Brehmer is clearly evident

It seems obvious that the rational and purposeful use of rest in pulmonary tuberculosis should be credited to Trudeau (Ref 55) rather than to Dettweiler The latter however clearly emphasized fresh air and the "outdoor life" and the morale factor in sanitarium life

Later Dettweiler ("Die Therapie der Phthisis" Verhandl d Kong f inn Med Wiesbaden 6 13 1887) gave a comprehensive lecture on treatment in which he emphasized the same points liberal upbuilding diet[2] fresh air morale and rest

Pratt a modern exponent of the home rest cure gives a fine summary of the whole subject (J H Pratt "The importance of prolonged bed rest in the treatment of pulmonary tuberculosis" *Am Rev Tuberc* 1 637 1917)

28 KOCH Robert Die Aetiologie der Tuberculose Berl klin Wchnschr 19 221 1882

Koch s work ranks with that of Laennec and Villemin as one of the greatest achievements in the study of tuberculosis Koch had convinced himself as a result of the work of Villemin of Cohnheim and of others that the dread disease was communicable and was caused by a living virus " The "bacteriological era" was at its peak and new organisms were being isolated right and left. Koch was the master technician he was an expert in staining and in pathological tissue technique He deliberately set about to demonstrate the organisms of tuberculosis which he felt must exist His first stroke of genius when ordinary stains showed nothing was to add potash to his methylene blue to intensify its effect and then there were revealed in tuberculous tissues of all sorts from man and animal many typical slender bacilli. Koch noted that these were usually "pure" and that no cocci of the common sort were present to indicate contamination

Koch then set about growing the bacilli He used coagulated serum (this was not his own idea) but again his genius was revealed by his patience in waiting several weeks for growth to occur All known bacteria at the time appeared in culture media within a few days if nothing was visible the cultures were usually discarded Just what went on in Koch s mind to make him preserve his cultures of tuberculous material and patiently wait for several weeks he does not say Perhaps he forgot to discard them or perhaps he did not know himself therein lay his genius

[2] A dinner at Falkenstein was as follows

December 16

Potato soup
Rabbit ragout with noodles
Filet sauté au madeire Cauliflower
Stewed duck salad compote
Apricot torte Fruit, etc

The next step was to inoculate by various routes—subcutaneous intraperitoneal intraocular—into animals bacilli which had been subcultured several times In all these elaborate and conclusive experiments typical tubercle was produced just as with inoculation of tuberculous material direct from lesions And finally tubercle bacilli were once more grown from the lesions produced by inoculation with pure cultures The paper is a masterpiece of exposition and does not leave much more to be said Indeed after Koch had read his report at the meeting of the Physiological Society in Berlin on March 24 1882 when the chairman called for discussion everyone was silent—even the great Virchow whose tenacious views about the non unity of tuberculous lesions were finally shattered

In his concluding remarks Koch pointed out that tubercle bacilli could be derived only from the animal organism and he believed that the portal of entry must usually be by inhalation of dust He found that *dry* sputa retained their virulence for several weeks Finally he pointed out the public health aspect and declared that the basic knowledge was now at hand for a logical and successful campaign against tuberculosis

An excellent and accurate translation of Koch s paper with a stimulating introduction by Allen Krause is to be found in the American Review of Tuberculosis (The aetiology of tuberculosis Dr Robert Koch a translation by Bertha Pinner and Max Pinner 24:285 1932)

29 [EHRLICH Paul] Aus dem Verein fur innere Medicin zu Berlin Sitzung vom 1 Mai 1882 (stenographic report of a talk by Ehrlich at the previous meeting) Deutsche med Wchnschr 8 269 1882

Ehrlich later to become renowned in the fields of immunity and chemotherapy was interested in stains probably through the influence of his cousin Weigert the pathologist Koch had hardly announced his work when Ehrlich set about to improve the difficult staining technique of tubercle bacilli He found that "anilinol added to a saturated alcoholic solution of fuchsin or methyl violet made an excellent stain It shortened the process by many hours and the specimens were better preserved He also established the principle of the acid fastness of tubercle bacilli by decolorizing his preparations with a mixture of one part of nitric acid and two parts of water and finding that the organisms remained brilliantly stained He pointed out that the capsule seemed impermeable to acid and that therefore alkalis should be effective in destroying the bacilli

F Ziehl ("Zur Farbung des Tuberkelbacillus Deutsche med Wchnschr 8 451 1882) modified the Ehrlich procedure by using carbolic acid instead of aniline and a weaker acid for decolorization The contemporary strivings for better straining methods are well summarized by B Frankel (Ueber die Farbung des Koch schen Bacillus und seine semiotische Bedeutung fur die Krankheiten der Respirationsorgane Berl klin Wchschr 21 193 1884)

We cannot go further into the staining and morphology of tubercle bacilli in this bibliography but the problem is fully discussed in H G Wells I M De Witt and E R Long *The Chemistry of Tuberculosis* (Baltimore Williams & Wilkins Co 1923) and in H S Willis and M M Cummings *Diagnostic and Experimental Methods in Tuberculosis* (Springfield Ill Charles C Thomas 1952)

30 FORLANINI C A contribuzione della terapia chirurgica della tisi Ablazione del polmone? Pneumotorace artificiale? Gazz d osp 3 537 585 601 609 617 641 657 665 689 705 1882[3]

Although there had been some previous suggestions (Ref 3) credit is generally given to Forlanini for popularizing the procedure of induced closed pneumothorax This his first paper or rather series of papers was however long rambling and philosophical with little factual material artificial pneumothorax by no means immediately came into popular use and it was only many years later that Forlanini s important monograph defining indications technique and results appeared (C Forlanini "Die Behandlung der Lungenschwindsucht mit dem kunstlichen Pneumothorax" Ergebn inn Med u Kinderh 9 621 1912) The whole subject is reviewed by Eli H Rubin (Pneumothorax treatment of pulmonary tuberculosis" Medicine 16:351 1937) with nearly three hundred references Forlanini s original paper has been translated into English (S Lojacano "Forlanini s original communication on artificial pneumothorax Tubercle 16 54 1934) Extra pleural pneumonolysis which falls in the domain of collapse therapy is comprehensively reviewed by Arthur H Aufses "Extrapleural pneumonolysis in the treatment of pulmonary tuberculosis' Medicine 18 129 1939

It is of interest that pneumothorax for so many years one of the mainstays of treatment in pulmonary tuberculosis is now (1951) becoming obsolete As the lush Mississippi steamboats vanished practically overnight when the railroad was built along the river so antibiotics and resection are rapidly crowding out pneumothorax the disadvantages of which are being more and more emphasized Actually Forlanini raised the question in 1882 of whether resection would not ultimately be an important method of therapy

The history of artificial pneumothorax in America is vividly told by James J Waring (J Outdoor Life 30 305 1933)

31 BOLLINGER O Ueber Tuberkelbacillen im Euter einer tuberculosen Kuh und uber die Virulenz des Secretes einer derartig erkrankten Milchdruse Arztl Intelligenzbl 30 163 1883

This brief paper was of fundamental importance in the controversy as to whether milk from tuberculous cows was a source of the disease Bollinger had already shown that a few drops of such milk sufficed on injection to kill a guinea pig in a few weeks He and his associates in the Munich Pathological Institute now examined a diseased udder from a tuberculous cow in the tissues and secretions of which they demonstrated innumerable bacteria which had all the characteristics of tubercle bacilli Lesions produced in guinea pigs by this material again showed typical tubercle bacilli

[3] Forlanini s articles on artificial pneumothorax actually appeared in the journal Gazzetta degli ospitali Curiously enough Lojacano states in his literal translation in Tubercle that the journal was the Gazetta degli ospa leli e delle cliniche di Milano of the same date This error has been repeated in the bibliography of Rubin s article The explanation of this odd mistake is that the Gazzetta degli ospitali in 1895 changed its name to the longer and more pompous title of Gazzetta degli ospedali etc The error is the same as giving credit to the New England Journal of Medicine for an article which appeared in its predecessor the Boston Medical and Surgical Journal

32 KOCH R Die Aetiologie der Tuberculose Mitt a d k Gsndhtsamte Berlin 2 1 1884

In this important article of eighty six folio pages Koch made his definitive presentation of the discovery and isolation of the tubercle bacillus and the proof of its causal relation to the disease It is really a masterful elaboration of his preliminary communication As Krause has well put it (J Outdoor Life 15:109 1918) "Years have slipped by since then and in this time a tremendous lot of grist has gone through the tuberculosis mill But today Koch s great work remains what it was when it first saw the light as regards the character and life history of the tubercle bacillus complete and unassailable in every detail, without a flaw without a leak to be plugged Koch also discussed the clinical and anatomical features of various forms of spontaneous tuberculosis in man and in animals This treatise is undoubtedly one of the great pieces of medical writing of all time It should be read and the beautiful plates examined by every doctor

33 STRASSMANN Fritz. Ueber Tuberculose der Tonsillen Virchows Arch f path Anat 96:319 1884

In any discussion of the portal of entry of the tubercle bacillus the question of tonsillar involvement is paramount Strassmann found a high incidence of small tubercles in the tonsils from cadavers which showed extensive lesions of various organs usually with cavitation of the lungs In only one case was caseation of glands of the neck noted In tonsils excised during life S J Crowe S S Watkins and A S Rothholz ("Relation of tonsillar and nasopharyngeal infections to general systemic disorders" Bull Johns Hopkins Hosp 28 1 1917) found that 4–8 per cent showed tuberculosis in some cases extensive and with caseation In over half the patients with tuberculous tonsils there was clinical evidence of tuberculous glands of the neck These observations emphasized the tonsil as perhaps an important portal of entry for the tubercle bacillus

34 BAUMGARTEN I Die Histogenese des tuberculosen Processes Centralbl. f klin Med 5 233 1884

By studying material derived from the anterior chamber of the eyes of rabbits which had been inoculated with tubercle bacilli Baumgarten gave the first comprehensive and correct interpretation of the histology of tubercle He showed that epithelial and giant cells arise from fixed tissue cells and not from the colorless blood corpuscles as had been previously claimed

Study of this subject has continued through the years (see for example Arthur J Vorwald "The early cellular reactions in the lungs of rabbits injected intravenously with human tubercle bacilli" *Am Rev Tuberc* 25 74 1932 Florence R Sabin Cellular studies in tuberculosis Am Rev Tuberc 25 153 Esmond R Long "The inflammatory reaction in tuberculosis" Am J M Sc 185 749 1933)

35 DE CERENVILLE [Edouard] De l intervention operatoire dans les maladies du poumon Rev méd de la Suisse rom 5 441 1885

It is difficult to trace priority in connection with thoracoplasty for tuberculosis since the procedure was really an outgrowth of the general concept of collapse

therapy Collapse operations also were not originally designed exclusively for tuberculosis but were tried in all sorts of pulmonary suppurations De Cerenville however clearly grasped the concept that rib resection might be practiced not only as an approach to drainage of a cavity but for its value as a collapse measure "Ablation of the ribs achieved an important mechanical effect This mechanical factor is the *retraction of the thorax* indispensable in certain instances for complete success" "In another case of tuberculous cavity with resection of two ribs the cavity was not opened Operation July 18 by July 28 the gap between the ends of the resected ribs had manifestly retracted." In another case after rib resection "The thorax showed a marked retraction in the zone corresponding to the cavity At the same time the cavity contracted" It must be remembered that this sort of eosurgery" was really ancillary to the primary objective of opening and draining cavities Nonetheless it was inevitable that De Cerenville's work should be followed by further development of thoracoplasty Everyone interested in the subject should study this paper H Quincke ("Zur operativen Behandlung der Lungenabscesse" Berl klin Wchnschr 25 349 1888) also recognized the importance of collapse although he was primarily interested in non tuberculous abscesses By 1890 Carl Spengler ("Zur Behandlung starrwandiger Hohlen bei Lungenphthise" Verhandl d Gesellsch Deutscher Naturforsch u Arzte 63 236 1890–91) clearly enunciated the principles of more modern therapy In cases of rigid cavities it was advisable to treat by "mobilization of the stiff walls in our case by rib-resection and mobilization of the thoracic wall that is by a thoracoplasty without opening the pleural cavity" Spengler seems to have been the first to use the term "thoracoplasty The next landmark in the subject was Brauer's comprehensive article (L Brauer Erfahrungen und Ueberlegungen zur Lungenkollapstherapie" *Beitr z. klin Tuberk* 12 49 1906) and to these should be added the authoritative review with their own contributions of F Sauerbruch and H Elving "Die extrapleurale Thorakoplastik" Ergebn inn Med u Kinderh 10 869 1913 The whole subject is well summarized in John Alexander *The Surgery of Pulmonary Tuberculosis* (Philadelphia Lea & Febiger 1925) and in Alexander's more recent comprehensive treatise *The Collapse Therapy of Pulmonary Tuberculosis* (Springfield Ill Charles C Thomas 1937)

We cannot attempt to refer to the colossal current literature which requires a special bibliography of its own

36 MARFAN A De l immunité conferee par la guerison d une tuberculose locale pour la phthisie pulmonaire Arch gen de med 157 423 1886

No sooner had the bacillus been discovered than many workers began to occupy themselves with the question of prevention and immunization of tuberculosis Marfan in a paper which is definitely a landmark pointed out that "local tuberculosis such as glands of the neck (scrofula) was really only a local manifestation of a "general infection and that one must not expect a complete cure by local excision He also noted that pulmonary tuberculosis was mild or absent in those having lupus or scrofula He raised the question "Will it be possible one day to vaccinate against tuberculosis? One day perhaps experiment will answer this question until now tuberculosis even attenuated is a disease too

serious with evolution too insidious and uncertain for one to attempt preventive inoculation." This was years before vaccination with BCG was tried (Ref 57)

37 CORNET Georg Die Verbreitung der Tuberkelbacillen ausserhalb des Korpers Ztschr f Hyg u Infectionskr., 5 191 1888

The discovery of the tubercle bacillus by Koch was greeted with high enthusiasm on all sides Soon however troubled thoughts arose It was believed at first that consumptives exhaled tubercle bacilli at every breath and that they might be projected into the air by wind currents blowing over sputum If this was so the inspired air and the environment in general must be full of bacilli all the time and how could anyone escape infection when one of every seven people already had consumption? In the near hysteria aroused by these views it was even proposed to ship all consumptives to an island isolated in mid-ocean.

These speculations however had the merit of arousing on all sides an acute awareness of the public health aspects of the problem and they stimulated a vast amount of experimental work. Cornet s paper or rather monograph since it occupies 141 pages explores the subject in great detail Cornet was a pupil of Koch, and this work was done under the master s sponsorship First others as well as Cornet showed that tubercle bacilli were not expelled on ordinary breathing and that moist sputum did not readily lead to clouds of bacilli in the air Cornet s main work, remarkable in extent and detail, consisted of collecting dust from walls and floors in the vicinity of coughing consumptives With this dust he was able by inoculation to produce tuberculosis in laboratory animals He also showed that dust from areas where there were no consumptives did not produce tuberculosis

Cornet enunciated the theory that tuberculosis of the lungs was acquired by the inhalation of bacilli swept up in dust containing dried sputum (Cornet s dust theory) While this view which was widely accepted, turns out of course to be true only in part if at all, it gave an immense impetus to study of the problem emphasized the danger of careless expectoration of sputum on floors into handkerchiefs etc and started the movements for sputum control and sterilization so important in tuberculosis The paper is especially outstanding because of the careful and thorough methods and the astute and detailed reasoning

38 GRANCHER J and MARTIN H Tuberculose expérimentale Sur une mode de traitement et de vaccination, Compt. rend Acad. d sc 111 333 1890

After the discovery of the bacillus many workers tried every conceivable method of "immunization" with preparations of tubercle bacilli of all sorts Grancher and Martin, although their experiments were primitive seemed to show that rabbits prepared by injections of attenuated bacilli (method of attenuation not clearly stated but suggested by Pasteur s rabies immunization) developed increased resistance to subsequent injections of virulent bacilli The validity of these observations cannot be tested now but they clearly anticipated later attempts at human immunization (Ref 57)

39 KOCH R I Weitere Mittheilungen uber ein Heilmittel gegen Tuberculose Deutsche med Wchnschr 16 1029 1890

This was the famous report which shook the medical world since Koch here claimed that the new preparation tuberculin[4] was a curative agent in tuberculosis Koch first discussed the subject at the International Medical Congress (Berlin August 4 1890) He stated in this paper that he did not intend to publish until his observations were complete but that irresponsible publicity had forced his hand Actually he said nothing about the preparation or composition of tuberculin he stated only that it was derived from cultures of the bacillus

Although Koch discussed the diagnostic value of his material and pointed out that recovery might be indicated by a waning reaction he considered the substance to be primarily a therapeutic agent He emphasized that it was ineffective when given by mouth No reaction occurred in healthy guinea pigs but Koch regarded this as a species difference between guinea pig and man He did not realize that a non tuberculous man would also not react and his healthy (*gesunde*) people who gave mild reactions of course had latent tuberculosis The classical symptoms of a tuberculin reaction following subcutaneous injection are graphically described and the specificity is emphasized

The conviction that tuberculin was a curative agent in tuberculosis was based primarily on observation of visible lesions such as lupus vulgaris "With these lesions changes occur which allow one to recognize a really surprising specific antituberculosis action" Koch then gave a graphic description of the sequence of events—exacerbation followed by crusting desquammation and healing by healthy scar Curative action was less dramatic with lymph node and bone lesions and the results with advanced consumption were dubious enough to make him admit that one could do better with the very early stages of pulmonary disease Koch also insisted that tuberculin did not kill the bacilli but only the living tuberculous tissue Dead tuberculous masses must either slough off or be removed surgically Throughout the paper one should remember that Koch had no idea of the concepts of hypersensitivity and allergy which were to be developed a few years later (Ref 48)

Koch closed on a conservative note He had to depend largely on the reports given to him by his clinical associates One reads between the lines that this sound and critical observer was not yet absolutely sure of his ground One may wonder whether he later regretted being forced into hasty publication of material not yet large enough for statistical analysis

40 TRUDEAU E L An experimental study of preventive inoculations in tuberculosis M Rec 38 565 1890

Only a few weeks after Koch had announced his great discovery (Ref 39) of cure and prevention of tuberculosis by "tuberculin Trudeau working obscurely in Saranac Lake and using essentially the same material as Koch published this important study in which he was unable to show any preventive effect of

[4] The term "tuberculin" was not used by Koch who spoke only of his curative material (*Heilmittel*) It was introduced later perhaps by Doutrelpoint (Deutsche med Wchnschr 17 348 1891) or perhaps by O Bujwid (Doswiadzenia na zwierzetach z tuberkulina Gaz lek Warszawa 2d ser 11 582 1891)

culture filtrates against experimental tuberculosis Trudeau was right and Koch was wrong no animal has ever been protected against tuberculosis by pretreatment with tuberculin This paper is also of interest because Trudeau describes the origin of the famous attenuated R_1 strain used for so many years in experimental tuberculosis

A little later (E L. Trudeau "The treatment of experimental tuberculosis by Koch s tuberculin etc " M News 61 253 1892) he concluded that "Koch s tuberculin does not cure experimental tuberculosis in the guinea pig " but he thought that experimental tuberculosis in the rabbit s eye could be healed by injections of the culture filtrates Trudeau did not of course understand at the time that success with tuberculin as a therapeutic measure depends on the character of the lesion and the setting up of just the right amount of reaction criteria which for the most part have rendered tuberculin impractical At about the same time as Trudeau points out W Donitz ("Ueber die Wirkung des Tuberculins auf die experimentelle Augentuberculose des Kaninchens " Deutsche med Wchnschr 17 1289 1891) reported on the cure by tuberculin of experimental tuberculosis of the anterior chamber of the eye in the rabbit "To get healing it is necessary to give increasing doses of tuberculin and for a long time to maintain a not too slight reaction "

41 KOCH R Fortsetzung der Mittheilungen uber ein Heilmittel gegen Tuberculose Deutsche med Wchnschr 17:101 1891

It is difficult now to appreciate the sensation made by Koch s announcement of a curative agent for tuberculosis (Ref 39) In this brief supplementary paper he again describes the classical experiment which led him to believe in its healing powers if a guinea pig with a tuberculous nodule of the skin from a first injection is reinjected with a suspension of tubercle bacilli the original nodule becomes acutely inflamed and necrotic but then leaves a clean ulcer which heals completely Since the injection of bacilli led at times to local abscesses Koch thought an extract of the organisms might suffice and in this paper he now divulges the nature of the curative agent "This substance is a glycerin extract of pure cultures of tubercle bacilli "

Meanwhile intensive clinical trials were being made by doctors to whom Koch furnished the material and in this volume of the Deutsche medizinische Wochenschrift (1891) there are no fewer than seventy four reports of its use under various circumstances on the patients who flocked from all sides Every one agreed on its great and specific value in diagnosis but there were many reservations and doubts about its therapeutic effects and some even declared that it was dangerous and furthered the tuberculous process

In still another paper Koch ("Weitere Mittheilung uber das Tuberculin *ibid* p 1189) provides details of the preparation of tuberculin and of attempts to purify it Injections were given to a number of healthy doctors who all "re acted " In trying to explain this Koch was again at a disadvantage in working before the elementary concepts of allergy had been defined.

An excellent early summary of the whole status of tuberculin is given in the monograph of L Hamman and E Wolman *Tuberculin in Diagnosis and Treatment* (New York D Appleton & Co 1912)

42 TUFFIER [Théodore] De la résection du sommet du poumon *Semaine méd* 2 201 1891

Aside from some primitive and unsuccessful attempts, Tuffier seems to have been the first successfully to extirpate part of a lung for tuberculosis The case is reported in detail and the patient was presented as cured In his comprehensive lecture before the Twelfth International Congress of Medicine in Moscow in 1897 ("Chirurgie du poumon en particulier dans les cavernes tuberculeuses et la gangrène pulmonaire" Compte rend du XII[e] Cong Internat de Méd Moscou 1897 p 5 pub S P Yakovlev Moscou 1899), Tuffier develops the whole subject of pneumonectomy which he amplified into his book, *Chirurgie du poumon* (Paris Masson et Cie 1897) It is of interest that the surgery of pulmonary tuberculosis in view of its present vogue was not pursued further for many years As recently as 1935 a report of lobectomy (S O Freedlander "Lobectomy in pulmonary tuberculosis" J Thoracic Surg 5 132, 1935) was hailed as an original achievement by those surgeons who discussed the paper The rapid development especially in very recent years (1950—) of lobectomy and segmental resection goes hand in hand with the availability of effective antibiotics (Ref 63)

There is now a large and rapidly growing literature which cannot be reviewed in detail and which is indeed still controversial (see for example Edward J O Brien *et al*, "The present chaos regarding resection of residual and caseous lesions in pulmonary tuberculosis J Thoracic Surg 26 441, 1953 J Maxwell Chamberlain Clifford F Storey Robert Klopstock, and Charles F Daniels "Segmental resection for pulmonary tuberculosis" J Thoracic Surg 26 471, 1953 300 cases Lyman A Brewer III Harlow W Harrison Rodney P Smith and Angel F Bai Indications for segmental resection in pulmonary tuberculosis Am Rev Tuberc 69 554 1954)

43 TRUDEAU E L Eye tuberculosis and anti tubercular inoculation in the rabbit Tr A Am Physicians 8 108 1893

Although Grancher and Martin (Ref 38) thought that they had produced resistance to tuberculosis by injection of "attenuated" strains of bacilli Trudeau s experiments were much more convincing After injecting avian bacilli into rabbits subsequent inoculations into the eye were made with strains derived from "tuberculous lesions of the rabbit" In the previously vaccinated animals injections of mammalian bacilli into the eye were followed by a sharp reaction often with subsequent recovery in distinction to progressive tuberculosis of the eye in the untreated controls Trudeau recognized that the immunity or resistance conferred was only partial "I do not lay claim therefore to have produced a complete or permanent immunity by a safe method" concluded this sound and careful investigator In a follow up study of these rabbits ("A report of the ultimate results obtained in experimental eye tuberculosis by tuberculin treatment and anti tubercular inoculation" Tr A Am Physicians 9 168 1894) Trudeau noted that the eye lesions recurred and progressed in many of the animals "The extent to which the tubercular process can be influenced favorably seems to depend rather upon the degree and character of the irritation induced about the tubercle than upon any direct germicidal effect or upon the production of a lasting immunity"

Trudeau sensed the fact that significant immunity could be stimulated only by the production of tubercle in the body (preferably with living bacilli) and that soluble culture products were ineffective

44 FLÜGGE C Ueber Luftinfection Ztschr f Hyg u Infectionskr 25 179 1897

Flugge and his associates convinced themselves that the transmission of tubercle bacilli dried in dust as promoted by Cornet (Ref 37) was not of practical importance in human pathology They thought it more likely that direct trans mission took place from person to person They were also aware as had been shown by others that the quietly exhaled breath was sterile and that actual particles of sputum or saliva must be expelled in order for bacteria to leave the respiratory passages This led to the development of Flugge s "droplet theory Even though it was shown that prolonged and close contact in direct line with the patient s cough was necessary in order to inhale any large number of bacilli Flugge concluded that pulmonary tuberculosis was most likely trans mitted by the inhalation of bacillus-containing droplets

It is in this paper that Flugge laid the experimental groundwork for the droplet theory During the next few years a large number of papers appeared in the same journal by Flugge ("Die Verbreitung der Phthise durch staub formiges Sputum und durch beim Husten verspritzte Tropfchen" Ztschr f Hyg u Infectionskr 30 107 1899) and by his associates probing every con ceivable phase of transmission of bacterial infection One particularly important paper was that of Bruno Heyman ("Ueber die Ausstreuung infectioser Tropf chen beim Husten der Phthisiker" Ztschr f Hyg u Infectionskr 30 139 1899) who demonstrated the great difficulty of infecting guinea pigs by having consumptives cough directly at them In spite of this the droplet theory was widely accepted at the time An authoritative and critical analysis of this whole problem is to be found in Allen Krause s Essays on tuberculosis VII Infection by inhalation Flugge s theory of droplet infection" J Outdoor Life 15 225 1918

45 SMITH Theobald A comparative study of bovine tubercle bacilli and of human bacilli from sputum J Exper Med 3 451 1898

Koch believed that all tubercle bacilli from mammalian sources were the same "species and this view was generally held until the work of Smith In a report before the Association of American Physicians ("Two varieties of the tubercle bacillus from mammals" Tr A Am Physicians 11 75 1896) he studied a strain of the bacillus from a tuberculous raccoon presumably infected from a human source and a strain from a tuberculous bull Striking differences were shown which were extended by the elaborate studies reported in the present paper Smith clearly defined the cultural and pathogenic differences (in guinea pigs in rabbits and in cattle) which are standard knowledge today He opened the way for clarification of human infection with bovine strains "Now that we have established some differences between bovine and sputum bacilli the time has come to study with care the tubercle bacilli from cases of supposed animal origin so that some basis may be found upon which to found statistics It will take much time In the meantime the relation

of bovine to human tuberculosis must be somehow defined before a fairly helpless and frightened public Smith s work explained many previously per plexing problems such as the difficulty of producing tuberculosis in cattle with material from human sources

46 FRANKEL Albert Das Tuberculinum Kochii als Diagnosticum Ztschr f Tuberk 1 291 1900

The significance of the tuberculin reaction was greatly confu ed by the occur rence of many positive reactions in apparently healthy men E Peiper for example ("Ueber die Wirkung des Koch schen Mittels auf gesunde oder nich tuberculose Individuen" Deutsche med Wchnschr 17:160 1891) with this point in mind found that eighteen of twenty two patients with absolutely no evidence of tuberculosis gave positive reactions The obvious solution of this paradox was autopsy material which would give a more accurate idea of the presence of tubercle than would clinical examination The first comprehensive studies were made in cattle Frankel collected the results of eight thousand autopsies In only an occasional case (2–3 per cent) was there a discrepancy between the tuberculin test and the anatomical findings This suggested that the (apparently) healthy people who reacted to tuberculin were nonetheless infected and harbored anatomical tuberculosis Frankel s results were promptly confirmed by others

47 NAGELI Otto Ueber Haufigkeit Localization und Ausheilung der Tuberculose Virchows Arch f path Anat 160 426 1900

Although the frequency of tuberculous foci in miscellaneous autopsy material was being recognized Schlenker (Virchows Arch of path Anat 134 145 1893) made the first purposeful study in 100 autopsies he found tuberculous foci in 66 It was the classical studies of Nageli however which really settled the matter in man as Frankel (Ref 46) had in cattle Nageli reported 508 careful autopsies in 406 there was evidence of tuberculous infection Among 420 adults 93 per cent had tubercle Later A Burkhardt ("Ueber Haufigkeit und Uhrsache menschlicher Tuberculose auf Grund von ca 1400 Sectionen," Ztschr f Hyg u Infectionskr 53 139 1906) published more extensive statis tics and pointed out the almost universal finding of tuberculous foci in adults the infrequency of such lesions in small children but the very high death rate from tuberculosis in early adult life The findings in children were extended by the careful studies of F Hamburger (Wien klin Wchnschr 20 1069 1907)

All this work explained the apparent paradox of the tuberculin test "healthy" people who reacted were actually infected and harbored tuberculous foci

48 LOWENSTEIN E and RAPPAPORT E Ueber den Mechanismus der Tuberculinimmunitat Ztschr f Tuberk 5 485 1904

It is hardly worthwhile going into the early (and erroneous) views as to the nature of the tuberculin reaction They are well reviewed by Hamman and Wolman (Ref 41) It was not until the pioneer work on anaphylaxis and hypersensitivity of Richet and Portier ("De l action anaphylactique de certains venins" Compt rend Soc de biol. 54 170 1902) or Arthus (Infections répétées de sérum de cheval chez le lapin" Compt rend Soc de biol. 55 817

1903) and of Von Pirquet and Schick ("Zur Theorie der Inkubationszeit" Wien klin Wchnschr 16 1244 1903) that the groundwork was laid for an understanding of the tuberculin reaction The vast contemporary literature on anaphylaxis cannot be further enumerated here While Von Pirquet and Schick Von Behring and others were evidently aware of the resemblance of the tuberculin reaction to hypersensitivity Lowenstein and Rappaport seem to have been the first to discuss clearly the mechanism in immunological terms and to define it as a hypersensitive reaction rather than a cumulative effect. Here again the early work was followed by an immense and at points controversial literature

49 VON PIRQUET, C Der diagnostische Wert der kutanen Tuberculinreaktion bei der Tuberculose des Kindesalters auf Grund von 100 Sektionen Wien klin. Wchnschr **20:1123** 1907

No procedure has been more important in the study of immunity and epidemiology of tuberculosis than the tuberculin skin test In this definitive paper Von Pirquet compared the results of his test with autopsies in 100 children Detailed results and case reports are given Von Pirquet recognized the significance of variations in the strength of tuberculin that a high dilution might give no skin reaction when more concentrated material gave a positive test He found that most of the negative tests were in very young children and in general showed that skin tests ran parallel with the results of general tuberculin reactions The specificity of the procedure was clearly proved As far as we can find out Von Pirquet s first published note on the skin test was a report before the Berlin Medical Society May 8 1907 ("Tuberculindiagnose durch cutane Impfung" Berl klin Wchnschr **44** 644 1907) He said that the test was suggested by the immediate reaction to smallpox revaccination and he described the technique of applying the tuberculin.

In 1908 G Mantoux ("Intradermo-réaction de la tuberculine Note de M Ch Mantoux présentée par M E Roux" Compt rend Acad d sc **147** 355 1908) described the intradermal tuberculin test which subsequently became standard practice in place of Von Pirquet s method

50 HAMBURGER Franz Ueber die Wirkung des Alttuberculins auf den tuberculosefreien Menschen Munchen med Wchnschr **55** 1220 1908

It took a long while before there was general acceptance of the principle that a positive tuberculin reaction depended on the presence of specific tubercle in the body Newborn babies who did not react were thought to have a peculiar resistance to tuberculin and it was not fully understood that absence of reaction in them was due to absence of tubercle Hamburger s studies were definitive He gave to children who had negative cutaneous tests as much as 500 mg of O T with no reaction of any sort These studies along with anatomical examinations made it obvious that resistance to tuberculin reaction was due to the absence of infection

51 ROMER Paul H Spezifische Ueberempfindlichkeit und Tuberculoseimmunitat Beitr z klin Tuberk **9** 79 1908

Work on hypersensitivity and on the tuberculin reaction led almost imperceptibly to the problem of immunity in tuberculosis The extensive original studies on hypersensitivity are reviewed in this classical paper by Romer and the applications to tuberculosis are discussed The early observations dealt largely with resistance to reinfection The problem was further studied by Romer and Joseph in a series of beautifully controlled experiments ("Die Tuberculose Reinfection" Beitr z klin Tuberk 17 287 1910) Whether the mechanism of immunity was associated with the allergic reaction of reinfection as Romer believed was for years vigorously debated and was strongly supported in America by A Krause (Ref 59) until Rich (Ref 60) emphasized that the two phenomena—allergic reaction and immunity—could be dissociated

Romer and Joseph concluded that immunity in tuberculosis was a specific allergic phenomenon conditioned by the character of the original infection and by the size and circumstances of the reinfecting dose

There were, however even in the early days of the subject conservative individuals who felt that allergy and immunity were not necessarily the same (see e g the important paper of F Hamburger "Ueber Tuberculoseimmunitat Beitr z klin Tuberk 12 259 1909)

52 PARK William H and KRUMWIEDE Charles Jr The relative importance of the bovine and human type of tubercle bacilli in the different forms of tuberculosis *J M Research 27 109 1912*

Beginning with Koch (Ref 28) a huge controversial literature grew up as to whether bovine tuberculosis was caused by a different race of bacilli from the human disease and whether man could acquire tuberculosis from animals Although many contradictions were answered by T Smith s studies (Ref 45) the definitive report of Park and Krumwiede demonstrated beyond question that the bovine bacillus was at fault in a high percentage of cases of tuberculosis in children who had ingested cow s milk in intestinal tuberculosis and in tuberculosis of the glands of the neck Elaborate tables are given which cannot be reproduced here but sample figures of infection with bovine bacilli in children under five years of age are as follows pulmonary 2 8 per cent cervical adenitis 61 per cent abdominal tuberculosis 58 per cent All this seemed finally to show that tuberculosis could result from either inhalation or ingestion and that it might be caused by either human or bovine bacilli With the elimination of infected milk tuberculosis of the glands of the neck" and abdominal tuberculosis have largely disappeared. A later careful study along similar lines is that of R M Price Summary of a study of the types of tubercle bacilli isolated from human lesions" Am Rev Tuberc 25 383 1932

53 GHON Anton Der primare Lungenherd bei der Tuberculose der Kinder Berlin and Vienna Urban & Schwartzenberg 1912

This book profusely illustrated and documented by innumerable autopsy reports is a classic in the field of the primary tuberculous lung lesion of childhood Ghon emphasized the need of very careful search for the primary lesion which might be in any part of the lung and the associated hilar adenopathy So fundamental were these studies that such a lesion is still often spoken of as a "Ghon focus or a "Ghon tubercle" But see Parrot (Ref 25)

54 SAUERBRUCH F Beeinflussung von Lungenerkrankungen durch kunstliche Lahmung des Zwerchfells (Phrenicotomie) Munchen med Wchnschr 60:625 1913

Although Stuertz ("Künstliche Zwerchfellahmung bei schweren chronischen einseitigen Lungenerkrankungen" Deutsche med Wchnschr 37:2224 1911) appears to have suggested artificial paralysis of the diaphragm for chronic uni lateral lung disease Sauerbruch seems to have been the first to report phrenic nerve section in tuberculosis It was not until some years later that Goetze advocated more effective paralysis by phrenic exairesis The attention which was paid to this method of therapy will be appreciated if one reads A H Aufses monograph "Phrenic nerve operations in the treatment of pulmonary tuberculosis" Medicine 16 139 1937 which includes 593 references

55 TRUDEAU Edward Livingston An autobiography Philadelphia and New York Lea & Febiger 1916

This book is a really great piece of biographical writing it ranks in our opinion with Lockhart s *Scott* Southey s *Nelson* and Trevelyan s *Macaulay* for its charm and vividness No chronicle furthermore could be of more interest to the student of tuberculosis recapitulating as it does that exciting era of the 1880 s when the bacillus was discovered and real knowledge of the disease began to advance

Trudeau was the founder of the sanitarium movement in this country al though influenced by Brehmer and Dettweiler (Refs 15 27) he learned the value of rest from his own case when over and over as he so vividly tells effort was followed by fever and prostration A pioneer in the cultivation of the bacillus and in the study of experimental tuberculosis it is interesting to hear how long it took after Koch s discovery—eight or nine years—before doctors in general accepted the little red rods as the cause of consumption Trudeau s scientific work perhaps not sufficiently recognized was of the highest caliber and was a real contribution to the understanding of tuberculosis the Saranac Laboratory with E Baldwin A Krause and others soon was recognized for its fundamental work.[5] But even today with chemotherapy and lobectomy the principles of rest and hygiene developed at the Adirondack Cottage Sanitarium are still paramount in the management of tuberculosis

56 OPIE Eugene L. The relation of apical tuberculosis of adults to the focal tuberculosis of children J Exper Med 26 263 1917

Following the early work on resistance (Ref 51) it was generally believed that adult tuberculosis occurred not by reinfection from the outside (because the patient had immunity from his childhood infection) but by autoinfection from a focus already present Attention came to be devoted not so much to external sources of contagion as to mechanisms of alleged lowering of resistance which allowed extension from the subject s already existing though perhaps latent focus This point of view for a long time inhibited proper epidemiological studies and effective public health measures

[5] Much of this wo k is reviewed in Edward R Baldwin S A Petroff and Le Roy S Gardner *Tuberculosis Bacteriology Pathology and Laboratory Diagnosis* (Phil delphia Lea & Febiger 1927)

Opie following Ghon (Ref 53) (see also "The focal pulmonary tuberculosis of children and adults" J Exper Med 25:855 1917) reinvestigated the incidence and character of childhood lesions and of adult tuberculosis by meticulous anatomical studies as well as by X rays of lungs removed at autopsy These studies led Opie to the conclusion that apical tuberculosis of adults is not the result of infantile tuberculosis but is caused by subsequent infection A complete investigation of ideas of reinfection followed and Opie s views were supported (Ref 61) by meticulous epidemiological studies

Some other workers held views similar to Opie s however and J Orth for example summarized his position (*Ueber einige Tuberculosefragen* [Jena Gustav Fischer 1918]) by saying It is wrong that the idea of exogenous infection should be held in discredit by some since its existence is unfortunately only too certain as the frequent tuberculous illnesses of nurses and attendants bear witness

57 CALMETTE A GUERIN K. NEGRE L and BOQUET A Prémunition des nouveau nés contre la tuberculose par le vaccin BCG (1921 à 1926) Ann Inst Pasteur 40:89 1926

In this article Calmette and his associates set forth the philosophy and the technique of protective vaccination with a living attenuated bovine bacillus (BCG) Although trials are being continued today (1957) there is still no entire agreement as to its practical value The difficulty with all procedures of this sort is that if the "immunizing dose is too small inadequate protection is conferred if it is too large there is danger of producing progressive tuberculosis The difficulties in standardizing the vaccine and of interpretation of results are also great—hence the conflicting claims and results Calmette elaborated this report in another article ("Sur la vaccination préventive des enfants nouveau nés contre la tuberculose par le BCG Am Inst Pasteur 41 201 1927) and shortly after gave an English summary (A Calmette and Harry Plotz "Protective inoculation against tuberculosis with BCG" Am Rev Tuberc 19 567 1929)

For a review of the whole subject see K N Irvine *B C G Vaccination in Theory and Practice* (Oxford Humphrey Milford 1949) R Dubos has authoritatively summarized the immunological aspects of BCG vaccination (Am Rev Tuberc 60 670 1949) Recent elaborate studies with attempts at careful control are reported by Aronson and his associates (Samuel C Stein and Joseph D Aronson "The occurrence of pulmonary lesions in BCG-vaccinated and unvaccinated persons" Am Rev Tuberc 68 695 1953 Joseph D Aronson and Charlotte Ferguson Aronson "The correlation of the tuberculin reaction with roentgenographically demonstrable pulmonary lesions in BCG vaccinated and control persons" Am Rev Tuberc 68 713)

58 OPIE Eugene L and McPHEDRAN F Maurice The contagion of tuberculosis Am Rev Tuberc. 14 347 1926

Following the work of Opie (Ref 56) Opie and McPhedran using tuberculin tests X rays and meticulous follow up procedures studied the contagion of tuberculosis in families They showed that when latent tuberculosis especially as revealed by X ray is taken into consideration "tuberculosis exhibits the

characteristics of a contagious disease" While latent lesions could by extension lead to spread even to other organs adult infection seemed to be usually acquired from external sources and not by spread of the subject s "childhood lesion Opie s many important studies are summarized in his papers Pathology of the tuberculosis of childhood and its bearing on clinical work," Brit M J 2 1130 1927 and "The pathogenesis of and transmission of tuberculosis" Am J M Sc 179:104 1930 He emphasized especially the importance of the latent lesion—without symptoms or physical signs—revealed by tuberculin tests and X rays in the pathogenesis of overt clinical tuberculosis In this connection E M Brieger s book *The Papworth Families* (London W Heinemann Ltd 1944) is of interest.

59 KRAUSE Allen K The dissemination of tubercle bacilli in the immune guinea pig with a discussion of the probable factors involved in tuberculo immunity Am Rev Tuberc. 11:211 1926

During the early decades of the century an immense amount of work was done on the problem of immunity to tuberculosis Krause working first at the Saranac Laboratory and later at the Kenneth Dows Laboratory in Baltimore dominated this field in America because of his ingenious and elaborate experiments Krause following the classical observations of Romer (Ref 51) sustained the thesis that the allergic reaction associated with reinfection fixed bacilli at their portal of entry and largely prevented invasion and spread This he considered the essence of immunity and in his conclusions to this paper he said "It is believed more probable that upon being re-infected the tissues of the immune guinea pig react promptly with some process that serves to impede the further passage of bacilli" "It is submitted that this process is the allergic exudative or inflammatory reaction which invariably sets in upon re infection of the tuberculous immune guinea pig which is otherwise normal" Innumerable papers by Krause and his associates dealing with this subject are to be found in the American Review of Tuberculosis from 1918 to 1928 Of special importance are the following H S Willis "The early dissemination of tubercle bacilli after intracutaneous inoculation of guinea pigs of first infection 11 173 1925 "The early dissemination of tubercle bacilli after intracutaneous inoculation of immune guinea pigs of reinfection" p 185 A K Krause and H S Willis "The influence of frequently repeated reinfection on allergy and immunity in tuberculosis" 14 316 1926 Even though they thought it paramount, they did not believe of course that the allergic reaction of reinfection was the only influence involved in resistance and they did much work on dose of bacilli environment and other factors Krause s associate H S Willis ("The waning of cutaneous hypersensitiveness of tuberculin and the relation of tuberculo immunity to tuberculo-allergy" Am Rev Tuberc 17 240 1928) even showed in guinea pigs that cutaneous allergy might wane and that "notwithstanding this greatly reduced and practically absent allergy such guinea pigs at thirty months after infection were found to possess a high specific immunity to re infection with virulent tubercle bacilli a finding hard to reconcile with Krause s thesis

Krause held sway over tuberculosis research in America for a good many

years and his views were widely accepted In addition to being a great scientist he was a man of brilliant and convincing personality The objective quality of his experiments leaves them unimpaired although his main thesis first systematically questioned by Rich (Ref 60), has now been weakened

60 RICH Arnold Rice and McCORDOCK Howard A An enquiry concerning the role of allergy immunity and other factors of importance in the pathogenesis of human tuberculosis Bull Johns Hopkins Hosp 44 273 1929

In this extensive critical analysis the prevailing view (Ref 59) that immunity in tuberculosis was effected by the allergic reaction of reinfection was challenged by Rich, who adduced an impressive collection of evidence to the contrary This article was subsequently elaborated into Rich s monumental monograph on *The Pathogenesis of Tuberculosis* (Ref 67) Rich s views were further exposed in another article ("The role of allergy in tuberculosis" Arch Int Med 43 691 1929) In subsequent papers (Arnold R Rich Frederick B Jennings Jr, and Lillian M Downing "The persistence of immunity after the abolition of allergy by desensitization Bull Johns Hopkins Hosp 53 172 1933 Herbert Rothschild Jonas S Friedenwald and Clarence Bernstein "The relation of allergy to immunity in tuberculosis Bull Johns Hopkins Hosp, 54 232 1934) experimental evidence was produced to show that immunity was unimpaired in animals desensitized so that no recognizable allergic reaction any longer occurred From this time on little was heard of the view that the allergic reaction of reinfection was the mechanism of immunity

61 HETHERINGTON H W McPHEDRAN F Maurice LANDIS H R M and OPIE Eugene L *Tuberculosis in medical and college students* Arch Int Med 48 734 1931

The work of Opie and his associates in which the acquisition of tuberculosis of adults by reinfection from the outside rather than by endogenous flareup of an old lesion was stressed (Ref 56) was followed by the development of intensive methods of case finding among various groups using tuberculin skin tests X rays of the chest and to a lesser extent physical examination and search for bacilli We cannot review here the vast literature on mass surveys The subject is covered in Herbert R Edwards monograph *Tuberculosis case finding studies in mass surveys* (Suppl to Am Rev Tuberc Vol 41, 1940)

The question of whether medical students and nurses are particularly liable to contract tuberculosis is however of immediate practical importance to the student of the epidemiology of the disease Hetherington and his associates seem to have been the first systematically to investigate this subject They found a rapidly increasing incidence of apical lesions in medical students and concluded that "they were peculiarly subject to advanced tuberculous infection

Here again a vast amount of similar work has been and is being done the general implication of which is that medical students and nurses acquire tuberculosis by contagion with greater frequency than does the population in general The studies of J A Myers and his associates carried the subject forward ("Tuberculosis among students and graduates of medicine" Ann Int Med 14 1575 1941 "Tuberculosis among students and graduates in nursing" *ibid*

p 873 1940) but the immense literature cannot be further reviewed here A recent study with a plea for standardized comparable methods in case finding is that of R Bates and W Davey ("Tuberculosis in medical and nursing students" Am Rev Tuberc 63 332 1951) The subject has also been thoroughly re viewed by Eleanor C Connolly in *Tuberculosis among Hospital Personnel* (New York National Tuberculosis Association 1950)

62 FELDMAN W H and HINSHAW H C Effects of streptomycin on experimental tuberculosis in guinea pigs a preliminary report Proc Staff Meet Mayo Clin 19 593 1944

The subject of the chemotherapy of tuberculosis really requires a bibliography of its own Numerous trials have been made in the past with all sorts of agents including gold salts derivatives of the sulfonamide group and many others Indeed no sooner had the bacillus been discovered than the dream of the physician was to find some substance which would destroy the bacillus in the human body Trudeau (Ref 55 p 204) tells graphically of his early attempts to cure tuberculous rabbits and guinea pigs by injections of creosote carbolic acid and other germicides But always "the tubercle bacillus bore cheerfully a degree of medication which proved fatal to its host!

The era of modern effective chemotherapy begins with the work of Feldman and Hinshaw Following the finding of S Waksman and others that strepto mycin had bactericidal effects on a strain of *Mycobacterium tuberculosis* in the test tube they tried this agent in guinea pig tuberculosis Only enough strepto-mycin was at first available to treat four animals but there was a striking result The material (75 mg daily per guinea pig) did not seem toxic and the lesions were absent or insignificant in the treated compared with the untreated con trols A second experiment confirmed the first The writers are to be commended for their conservative conclusions Streptomycin is an antibiotic substance well tolerated by guinea pigs which is capable under the conditions imposed of creating a striking suppressive effect on the pathogenic proclivities in guinea pigs of the human variety of Mycobacterium tuberculosis"

63 HINSHAW H C and FELDMAN W H Streptomycin in treatment of clinical tuberculosis a preliminary report Proc. Staff Meet Mayo Clin 20 313 1945

Although the first observations in man were made with small amounts of the early material, the writers believed that it produced "a limited suppressive effect Again they are justified in their caution they did not wish to disappoint countless hopeful patients by too enthusiastic statements

By 1953 standardized schemes of antibiotic therapy of tuberculosis had been worked out as may be read for example in the *Transactions of the 12th Con ference on the Chemotherapy of Tuberculosis* sponsored by the Veterans Ad ministration the Army and the Navy (1953) But the last word has not yet been said on the ultimate potentialities of these forms of therapy (see "Chemo therapy of tuberculosis in man Present status Report to the Council on Phar macy and Chemistry" prepared by Nicholas D Esopo J A M A 154 52 1954)

64 LEHMANN Jorgen Para aminosalicylic acid in the treatment of tuber culosis Lancet 1 15 1946

In previous work on the intermediate metabolism of tubercle bacilli (*ibid* p 14) Lehmann concluded that derivatives of salicylic acid might be effective in inhibiting growth In investigating many synthetic substances he found that p aminosalicylic acid produced definite inhibition The material was found to have little toxicity for rat guinea pig or man and early trials suggested that it might have a therapeutic effect in clinical tuberculosis After 10–14 gm a day by mouth temperature fell and this effect was not thought due to a non-specific antipyretic action Later work has of course confirmed the value of p aminosalicylic acid as a useful agent in the therapy of tuberculosis especially in association with other antibiotics such as streptomycin An excellent review is that of E Bogen R N Loomis and W W Drake Para aminosalicylic acid treatment of tuberculosis" *Am Rev Tuberc* **61** 226 1950

65 DUBOS René J Rapid and submerged growth of mycobacteria in liquid media *Proc Soc Exper Biol & Med* **58** 361 1945

Although many attempts had been made to devise a satisfactory medium for the growth of tubercle bacilli the difficulties were such that inoculation of guinea pigs with suspected material remained the standard method of isolation Dubos made the important discovery that addition to Long s synthetic medium of various lipids natural and synthetic allowed very rapid and diffuse growth of tubercle bacilli In numerous subsequent papers by Dubos and his associates this brief note is amplified (for references see Dubos "The tubercle bacillus and tuberculosis" *Am Scientist* **37** 353 1949)

Dubos methods have made practicable the routine use of cultures for the isolation of tubercle bacilli

66 MIDDLEBROOK Gardner DUBOS René J and PIERCE Cynthia Virulence and morphological characteristics of mammalian tubercle bacilli *J Exper Med* **86**:175 1947

Although previous attempts had been made to correlate growth characteristics and virulence Dubos and his associates gave the first clear demonstration In a synthetic medium containing a wetting agent "Tween 80" virulent cultures tended to form microscopically demonstrable serpentine cords of varying thickness and length consisting of highly acid fast bacilli oriented along the long axis of the cord Avirulent bacilli grow in a more or less nonoriented fashion They have never been observed to form cords" In this connection one should refer to the monograph by William F Drea and Anatole Andrejew *The Metabolism of the Tubercle Bacillus* (Springfield Ill Charles C Thomas 1953)

67 RICH Arnold R The pathogenesis of tuberculosis Springfield Ill Charles C Thomas 1944 2d ed 1951

This monumental book is an important milestone in the literature on tuberculosis It represents a critical analysis of resistance infection immunity and hypersensitivity from every possible standpoint documented with fifteen hundred references While reviewers have differed with Rich on small points all agree on the great skill with which a vast amount of material has been synthesized Every serious student of tuberculosis must carefully study this outstanding monograph

68 BERNSTEIN Jack LOTT William A STEINBERG Bernard A and YALE Harry L Chemotherapy of experimental tuberculosis V Isonicotinic acid hydrazide (Nydrazid) and related compounds Am Rev Tuberc 65:357 1952

"A class of compounds showing high antituberculous activity is reported for the first time Of these the most active is isonicotinic acid hydrazide (Nydrazid) In a standardized infection of mice with the Ravenal strain of M tuberculosis the minimal effective dose of this compound is 1/700 that of p-aminosalicylic acid" This experimental work in mice was soon followed by a flood of clinical reports (Ref 69) The situation is somewhat confused since two pharmaceutical houses seem to have developed the same compound practically simultaneously A number of other articles on the pharmacology of these compounds and on their effects in experimental tuberculosis are to be found in this same number of the review (April 1952)

69 ELMENDORF DuMont F Jr CAWTHORN William V MUSCHENHEIM Carl and McDERMOTT Walsh The absorption distribution excretion and short term toxicity of isonicotinic acid hydrazide (Nydrazid) in man Am Rev Tuberc 65:429 1952

These workers made a thorough study of the above points in tuberculous patients over periods of from 4 to 16 weeks They found the drug well tolerated but thought that it was not possible from their observations to "make any positive statement concerning the therapeutic value of this compound in the treatment of tuberculosis Meanwhile E Robitzek and I Selikoff ("Hydrazine derivatives of isonicotinic acid [Rimifon Marsilid] in the treatment of active progressive caseous pneumonic tuberculosis" Am Rev Tuberc 65:402) publishing at the same time found that these compounds "exert an impressive therapeutic effect Slightly antedating these were several reports in the Sea View Hosp Quart. Bull 13:3 12 17 27 and 52 1952

Current appraisal of izoniazid is well presented in "Present concepts of antimicrobial therapy in pulmonary tuberculosis (Am Rev Tuberc 68:819 1953) a panel discussion in which differences of opinion are freely expressed and in E A Riley s excellent review Chemotherapy of tuberculosis" (Am J M Sc 226 552 1953) However the whole subject is still in the investigative stage and the definitive bibliography must await the work of future years

70 LURIE Max B ABRAMSON Samuel and HEPPLESTON A G On the response of genetically resistant and susceptible rabbits to the quantitative inhalation of human type tubercle bacilli and the nature of resistance to tuberculosis J Exper Med 95 119 1952

We have given some of the early references on the development of ideas about immunity (Refs 51 59) In recent years the subject has been gone into more from the standpoint of the new views on antibodies which deal with them as concrete definable and measurable substances rather than the hypothetical lock and key pictographs of the Ehrlich side chain theory The present paper is given simply as an example of this sort of modern study it is of interest to note the reappraisal of allergy in relation to immunity

LEPROSY

Bacteriology	Refs 4 5 6
Clinical	Refs 1 8 10 11 12
General	Refs 1 8 10 11 12
Lepromin test	Ref 17
Pathology	Refs 3 7
Therapy chaulmoogra	Ref 2
Therapy general	Ref 10
Therapy streptomycin	Ref 16
Therapy sulfones	Refs 14 15
Transmission	Refs 1 6 7 9 10 13

LEPROSY

WHY the bibliography of leprosy presents an almost insuperable problem is not far to seek very few facts of the disease are settled and agreed upon by all workers—indeed almost every point is still in dispute Thus there is yet doubt whether the bacillus of leprosy has been artificially cultivated and whether the disease has actually been transmitted to animals The question of *communicability in man and the modes of adequate exposure are still unsettled.* Therapy even with the *modern* drugs *remains in a state* of trial and the results are extremely difficult to appraise As one goes through the literature then one can find no definitive papers on any of these points no one man who clearly proved anything Hence one must depend on critical discussions such as *are found in the books to which we refer below of various topics by experts* (who often disagree)

Few diseases have a more romantic past in legend and folklore than leprosy Most of the books enumerated here contain excellent historical sections especially that of Jeanselme (Ref 12) In addition, there are to be mentioned the interesting article by Sir James Y Simpson ("Antiquarian notes of leprosy and leper hospitals in Scotland and England" Edinburgh M & S J 56 301 1841 57 121 394 1842) and the tremendous compilation by R Virchow ("Zur Geschichte des Aussatzes besonders in Deutschland nebst einer Aufforderung an Aerzte und Geschichtsforscher" *Virchows Arch f path Anat* 18 138 273 19 43 1860 20 166 459 1861) both of which contain much source material A good brief historical discussion is that of Kaposi in F Hebra and M Kaposi s book *On Diseases of the Skin* (London New Sydenham Society 1875) p 115 *translated by Warren Tay* J Lowe s paper "Comments on the history of leprosy Indian M Gaz 77 680 1942 is also of interest The article on leprosy in August Hirsch, *Handbuch der historisch geographischen Pathologie* (2d ed Stuttgart Ferdinand Enke 1883) 2 1 contains much material of historical and epidemiological importance

As to bibliographies Danielssen and Boeck (Ref 1) give an interesting list of older titles whereas Babes (Ref 11) has a comprehensive bibliography to date In Jadassohn s monograph *Lepra* (Jena Gustav Fischer 1928) is an extensive reference list to titles after 1916 and McKinley s article (*Ref 4*) *is documented* by some five hundred references Bibliographies more or less extensive are also found in the books listed below However the monumental book by V Klingmuller (*Die Lepra* [Berlin Julius Springer 1930]) is what amounts to an annotated bibliography of the whole subject with sixty closely printed pages of references which the author has tried to make complete to 1930 The last chapter on "Lepra in literature and art by K Gron is of special interest Finally there should be mentioned the tremendous bibliography of leprosy (Luiza Keffer *Indice bibliográfico de lepra 1500–1943* [3 vols São Paulo Brazil 1944 1946 1948]) which requires three large volumes to cover all the references

There are a great many books and monographs dealing with the whole subject of leprosy Worthy of mention are of course Danielssen and Boeck s classic (Ref 1) and the treatises of G A Hansen and C Looft (*Ref 10*) J Jadassohn

(*loc cit*) E Jeanselme (Ref 12) R G Cochrane (*A Practical Textbook of Leprosy* [Oxford 1947]) and R Chaussinand (*La Lèpre* [2d ed Paris Expansion Scientifique Française 1955]) The standard work today is however that of L Rogers and E Muir (*Leprosy* [Baltimore Williams & Wilkins Co 3d ed 1946]) The precise brochure by H L Arnold (*Modern Concepts of Leprosy* [Springfield Ill Charles C Thomas 1953]) forms an excellent introduction to the subject The important topics of prophylaxis isolation and leprosaria are dealt with at length in Jeanselme (Ref 12, p 566) and in Cochrane (*op cit* p 191)

A great many journals are devoted solely to the subject of leprosy Of these some of the most important are the International Journal of Leprosy Manila sponsored by the International Leprosy Association the Leprosy Review London the British Empire Leprosy Relief Association Leprosy in India Calcutta Indian Leprosy Association and the Lepra Bibliotheca Internationalis Leipzig There are journals devoted to leprosy published in foreign languages such as the Leper Quarterly Shanghai sponsored by the Chinese Mission to Lepers and several South American journals

Finally there are transactions and reports of innumerable conferences and congresses on leprosy which have been held around the world from time to time

1 DANIELSSEN D C and BOECK Wilhelm Traité de la spédalskhed ou éléphantiasis des Grecs traduit du Norvégien sous les yeux de M D Danielssen par L A Cosson (de Nogaret) Paris J B Baillière 1848 (Original edition *Om spedalskheden* [Christiania 1847])

This monograph of some five hundred pages is generally accepted as the beginning of the modern study of leprosy Stimulated by and under the auspices of the Norwegian government Danielssen undertook to study leprosy in St George s Hospital in Bergen and like all studies based on careful observation of facts his turned out to be a valuable contribution Danielssen and Boeck divided cases of leprosy into the tuberculous form and the anesthetic form the former implicating especially the skin and the latter the nerves This classification with its sharp differentiation of two groups of cases has not quite stood the test of time but as a beginning it was useful "In the tuberculous form which has chosen the skin for the theater of its ravages we have the morbid changes exposed daily before our eyes In the anesthetic form which on the contrary affects by choice the centers of the nervous system we have found a series of very interesting nervous phenomena (Preface p xi)

Every aspect of the disease is discussed and documented by case reports "Under the heading of treatment of leprosy we have little to report" Arsenicals iodides and potassium salts are mentioned without much enthusiasm Bleeding was tried in some cases As to etiology the authors incline to accept heredity and to reject contagion There are few facts which are more commonly agreed on by authors ancient and modern than the transmission of the disease from parents to children [p 81] If we run through modern authors we find them almost unanimous on the non existence of any contagion (p 91) The views of Danielssen and Boeck had great influence on contemporary thought and led for

years to almost general acceptance of the theory that the disease was hereditary (see also Ref 13)

This interesting book which must be read to grasp its scope stands on the threshold of past and present Heavily documented, the ancient and old authors are constantly referred to while the carefully reported cases give a distinctly modern tone

2 MOUAT F J Notes on native remedies No 1 The chaulmoogra Indian Ann M Sc, 1 646 1854

The treatment of leprosy is very difficult to evaluate because of the long and variable course of the disease and the tendency to spontaneous remission Thus *post hoc* inferences have been common and chance faith and unknown variables have had an opportunity to influence judgment To conclude that a drug is effective therefore there should either be immediate improvement or if slow improvement should be marked Slight improvement coming over a long time means nothing As to the effects of the innumerable drugs and procedures which have been tried in leprosy, they are discussed in the sections on treatment in the various books listed in the introduction Sir Leonard Rogers ("Recent advances in the treatment and prophylaxis of leprosy Edinburgh M J 37 1 1930) writing fairly recently states that "the advances made in the treatment of leprosy in the last decade or so have opened up a new era of hope for the unfortunate leper and for the first time in three thousand years the disease has been known there are good grounds for believing that this dreaded disease will become greatly reduced"

However until the introduction of the sulfones (Ref 14) chaulmoogra oil or related substances were the backbone of drug therapy even though the results were variously judged by different observers Mouat turned his attention to native remedies in India and introduced the chaulmoogra into European practice The seeds[1] yield by expression a bland fixed oil with a peculiar and slightly unpleasant smell and taste with the faintest possible after flavour of the bitter almond It appears to have been long known to and prized by the Natives in the treatment of leprosy I was first informed of its value by Mr Jones the Headmaster of the Hindoo College at whose recommendation it was tried in the Leper Asylum with a favorable result" Mouat then reports three cases in which he thought that brilliant effects were obtained "With regard to the exhibition of the remedy it may be taken in the form of a pill or *the seed itself* *Six grains in the former case* or three seeds in the latter may be given daily In large quantity however it is apt to disagree causing nausea and irritability of the stomach A more elegant way of administering it would be in the form of the oil

The development of the use of chaulmoogra oil and its esters is fully discussed by L Rogers in the article referred to above

3 VIRCHOW Rudolph Die krankhaften Geschwulste 2 494 (article on leprosy) Berlin August Hirschwald 1864

In this interesting and scholarly article on leprosy Virchow's histological description of the lesions is of special interest Virchow discusses his "leprosy

[1] For beautiful photographs of the plant and its seeds see Jeanselme (Ref 12 pp 626 ff)

cells " "With reference to these cells I note that at the height of their development they consist of round pale faintly granular fragile elements with a moderately large and al o granulated nucleus In the fresh I was specially struck by their tendency to form a sort of vacuole probably through taking up water Their size is variable Many are not much larger than a red blood cell many reach the appearance of the largest mucous corpuscle [*Schleim körper*] "

4 HANSEN [Gerhard Henrik Armauer] Indberetning til det Norske medicinske Selskab i Christiania om en med understøttelse af selskabet foretagen reise for at anstille undersøgelser angående spedalskhedens årseger tildels udførte sammen med forstander Hartwig Norsk mag laegevidensk 3d ser 4:1 1874 (English translation I On the etiology of leprosy by G Armauer Hansen Brit & Foreign M Chir Rev 55 459 1875)

Hansen had been working on the bacteriology of leprosy for several years before he presented his paper at the medical society of Christiania Actually this long communication deals mainly with the question of whether or not leprosy is a hereditary disease It is not until the last page that an organism is mentioned "There are to be found in every leprous tubercle extirpated from a living individual small staff like bodies much resembling bacteria lying within the cells Though unable to discover any difference between these bodies and true bacteria I will not venture to declare them to be actually identical Further while it seems evident that these low forms of organic life engender some of the most acute infectious diseases the attributing of the origin of such a chronic disease as leprosy to the apparently same matter must of course be attended with still greater doubts It is worthy of notice however that the large brown elements found in all leprous proliferations in advanced stages of which I have in 1869 already given engravings bear a striking likeness to bacteria in certain states of development as these are represented by Klebs and further that in almost every preparation from a leprous tubercle made with the utmost care to avoid contamination and kept for a number of days in the damp chamber are developed conglobate masses of spherical bacteria or zoogloea "

What then was Hansen dealing with? Actually he seems himself in doubt—"unpregnant of his cause " and certainly Klebs who was nearly always wrong was an enthusiastic but unsound leader to follow

In his next communication Hansen (Bacillus leprae Virchows Arch f path Anat 79 32 1880)[2] opens by complaining that Dr Eklund, to whom he had shown his preparations and declared his views on the parasitic nature of leprosy had taken credit in a brochure Om spetelska " recently published for the discovery of a micrococcus in the tissues and that Dr Neisser from Breslau had visited in Bergen to study leprosy and had taken home material and published (Ref 5) to the effect that the preparations were everywhere loaded with bacteria which he as well as Ferd Cohn and Koch considered a new species and the cause of leprosy Thus Hansen felt that his hand had been forced and that he was obliged to publish his results more at length Hansen for the most

[2] This paper also appeared in English (G Armaner [*sic*] Hansen "The bacillus of leprosy Quart. J Micr Sc 20:92 1880) and in Norwegian (Bacillus leprae Nord med ark, 12 1 1880)

years to almost general acceptance of the theory that the disease was hereditary (see also Ref 13)

This interesting book which must be read to grasp its scope stands on the threshold of past and present Heavily documented, the ancient and old authors are constantly referred to while the carefully reported cases give a distinctly modern tone

2 MOUAT F J Notes on native remedies No 1 The chaulmoogra. Indian Ann M Sc 1 646 1854

The treatment of leprosy is very difficult to evaluate because of the long and variable course of the disease and the tendency to spontaneous remission Thus *post hoc* inferences have been common and chance faith and unknown variables have had an opportunity to influence judgment To conclude that a drug is effective therefore there should either be immediate improvement or if slow improvement should be marked Slight improvement coming over a long time means nothing As to the effects of the innumerable drugs and procedures which have been tried in leprosy they are discussed in the sections on treatment in the various books listed in the introduction Sir Leonard Rogers (Recent advances in the treatment and prophylaxis of leprosy" Edinburgh M J 37 1, 1930) writing fairly recently states that "the advances made in the treatment of leprosy in the last decade or so have opened up a new era of hope for the unfortunate leper and for the first time in three thousand years the disease has been known there are good grounds for believing that this dreaded disease will become greatly reduced

However until the introduction of the sulfones (Ref 14) chaulmoogra oil or related substances were the backbone of drug therapy even though the results were variously judged by different observers Mouat turned his attention to native remedies in India and introduced the chaulmoogra into European practice "The seeds[1] yield by expression a bland fixed oil with a peculiar and slightly unpleasant smell and taste with the faintest possible after flavour of the bitter almond. It appears to have been long known to and prized by the Natives in the treatment of leprosy I was first informed of its value by Mr Jones the Headmaster of the Hindoo College at whose recommendation it was tried in the Leper Asylum with a favorable result" Mouat then reports three cases in which he thought that brilliant effects were obtained "With regard to the exhibition of the remedy it may be taken in the form of a pill or the seed itself Six grains in the former case or three seeds in the latter may be given daily In large quantity however it is apt to disagree causing nausea and irritability of the stomach A more elegant way of administering it would be in the form of the oil"

The development of the use of chaulmoogra oil and its esters is fully discussed by L Rogers in the article referred to above

3 VIRCHOW Rudolph Die krankhaften Geschwulste 2 494 (article on leprosy) Berlin August Hirschwald 1864

In this interesting and scholarly article on leprosy Virchow s histological description of the lesions is of special interest Virchow discusses his "leprosy

[1] For beautiful photographs of the plant and its seeds see Jeanselme (Ref 12, pp 626 ff)

cells " "With reference to these cells I note that at the height of their development they consist of round pale faintly granular fragile elements with a moderately large and also granulated nucleus In the fresh I was specially struck by their tendency to form a sort of vacuole probably through taking up water Their size is variable Many are not much larger than a red blood cell many reach the appearance of the largest mucous corpuscle [*Schleim Korper*] "

4 HANSEN [Gerhard Henrik Armauer] Indberetning til det Norske medicinske Selskab i Christiania om en med understøttelse af selskabet foretagen reise for at anstille undersøgelser angående spedalskhedens årseger tildels udførte sammen med forstander Hartwig Norsk mag laegevidensk. 3d ser., 4 1 1874 (English translation I On the etiology of leprosy by G Armauer Hansen Brit. & Foreign M -Chir Rev., 55 459 1875)

Hansen had been working on the bacteriology of leprosy for several years before he presented his paper at the medical society of Christiania Actually this long communication deals mainly with the question of whether or not leprosy is a hereditary disease It is not until the last page that an organism is mentioned "There are to be found in every leprous tubercle extirpated from a living individual small staff like bodies much resembling bacteria, lying within the cells Though unable to discover any difference between these bodies and true bacteria I will not venture to declare them to be actually identical. Further while it seems evident that these low forms of organic life engender some of the most acute infectious diseases the attributing of the origin of such a chronic disease as leprosy to the apparently same matter must, of course be attended with still greater doubts It is worthy of notice however that the large brown elements found in all leprous proliferations in advanced stages of which I have in 1869 already given engravings bear a striking likeness to bacteria in certain states of development, as these are represented by Klebs and further that in almost every preparation from a leprous tubercle made with the utmost care to avoid contamination and kept for a number of days in the damp chamber are developed conglobate masses of spherical bacteria or zoogloea "

What, then was Hansen dealing with? Actually he seems himself in doubt—"unpregnant of his cause " and certainly Klebs who was nearly always wrong, was an enthusiastic but unsound leader to follow

In his next communication Hansen ("Bacillus leprae " Virchows Arch. f path. Anat. 79 32, 1880)[*] opens by complaining that Dr Eklund, to whom he had shown his preparations and declared his views on the parasitic nature of leprosy had taken credit in a brochure "Om spetelska," recently published, for the discovery of a micrococcus in the tissues and that Dr Neisser from Breslau had visited in Bergen to study leprosy and had taken home material and published (Ref 5) to the effect that the preparations were everywhere loaded with bacteria which he as well as Ferd. Cohn and Koch considered a new species and the cause of leprosy Thus Hansen felt that his hand had been forced and that he was obliged to publish his results more at length Hansen for the most

[*] This paper also appeared in English (G Armaner [sic] Hansen "The bacillus of leprosy" Quart. J Micr Sc., 20 92, 1880) and in Norwegian (Bacillus leprae" Nord. med. ark., 12 1 1880)

part examined scrapings of leprous material suspended in water and saw all sorts of granules and "bacteria Only one preparation after immersion in osmic acid and staining with methyl violet showed masses which seemed to consist of little rods "From the various notes of my investigations in 1873 every one will be easily able to see that I had good reason for supposing that bacteria appear in leprous products but also that I supported alone by these investigations could not propound a theory on this subject and still more decide whether these bacteria really were the virus which introduced into the system, produced the disease" The paper is dated October 1871 and there is a brief addendum I have succeeded after the suggestion of Dr Koch in seeing the bacilli beautifully in sections hardened in absolute alcohol and intensively stained They are present sometimes singly but usually in clumps which fits in with their occurrence *in* the cells" The drawings in Plate I are rather unsatisfactory and show nothing which could be identified as lepra bacilli It appears then that Hansen, like Jenner was inspired with an idea which turned out to be correct but he does not really present adequate evidence to support it

Earle B McKinley's monograph ("The etiology of leprosy" Medicine 13 377 1934) is a vast storehouse of information on the bacteriology cultivation and pathogenicity of the lepra bacillus documented by 525 references which supersedes any compilations previously published[*] McKinley summarized the vexed question of whether the bacillus had been successfully cultivated by saying "There does not exist today any absolute proof that any investigator has actually succeeded in the artificial cultivation of the leprosy bacillus" Furthermore Chaussinand quite recently (*op cit* p 33) in going over the subject, comes to similar conclusions "We have been able to show that Dubos medium which allows the cultivation of the tubercle bacillus in a few days in no way favors growth of the bacillus of Hansen"

5 NEISSER [A] Ueber die Aetiologie des Aussatses Jahresb d. Schles Gesellsch f vaterl Cultur 57 65 1879

Neisser tells the story of his trip to Norway to study leprosy He points out that most doctors following Danielssen believed that hereditary influences caused leprosy whereas the view of Hansen that the disease was contagious had practically no adherents Hansen had found conglomerate masses of bodies in leprosy tissue inoculation and culture experiments with which yielded no results "so that he was unable to conclude that he had before him the presumed virus of leprosy" Neisser took home much leprosy tissue in which with modern staining methods he saw innumerable "rods" There follows a detailed description of the organisms and of their relation to the tissue cells But "in anesthetic macroscopically undiseased skin, I could see neither bacilli nor any other pathological change I think that these bacilli are related to the pathological changes in Lepra in other words that Lepra is a bacterial disease The constancy of the finding of such a tremendous occurrence of this one form of bacillus in the most different organs speaks for my hypothesis"

In a second major paper Neisser ("Weitere Beitrage zur Aetiologie der Lepra," Virchows Arch f path Anat. 84 514 1881) straightens out the ques

[*] One is perplexed by the fact that in dealing with the discovery of the bacillus the work of Neisser is not even mentioned (see Ref 5)

tion of priority "When I was in Bergen in July and August 1879 Hansen had the idea that rodlike structures played a role in the cause of leprosy But even his colleagues in Bergen did not regard his findings as of any importance although they had been familiar with them for years Indeed some were antagonistic to the idea of contagion At the time there was no question of an actual bacillus and even less of staining and culture technique I take credit, therefore for establishing these bodies in their place as pathogenic bacteria since I was the first who applied in exact fashion the new staining methods of Weigert and Robert Koch and brought evidence that a specific variety of bacteria is concerned in leprosy which can be brought into causal relationship with all the pathological phenomena of the disease" There seems little doubt that Neisser deserves credit for going beyond the vague hypothetical stage and bringing real evidence Who should have priority for discovering the bacillus we leave to our readers to decide

Neisser found the bacilli in the skin lesions in the mucous membranes of the mouth, gums and larynx in the interstitium of peripheral nerves in the cornea cartilages testes lymph glands spleen and liver The bacilli were seen inside the large "lepra cells" described by Virchow (Ref 3) Neisser describes the histology of the lesions Some cells are stuffed with bacilli as shown with aniline stains Later the cells and bacteria disintegrate leaving the well known "vacuole formation" evident Very few bacilli occur outside cells in the connective tissue The bacilli are difficult to see unstained Tinctorial characteristics are described When properly stained the organisms appear as "fine slender rods of the length of one half to three-quarters of a human red cell." They are straight or slightly bent Some of the bacilli have round swellings at the ends or in the middle These Neisser regarded as spores His main argument that the bacilli were the cause of leprosy was their constant presence in all lesions as well as the histological appearance He thought the evidence favored lymphatic spread rather than hematogenous distribution "Leprosy is probably an infectious disease and its specific production is contagious" Contagion may be direct or indirect. "Leprosy according to my view is not transmissible by heredity Neisser thought that he had succeeded in culturing the bacilli although he was a little uncertain on this point. The paper contains so much material that the original must be read to get the full implications at any rate this is the first really adequate account of leprosy bacilli Neisser being wrong on only two points—the cultivability of the organisms and the idea that they formed spores

At about the same time confirmatory notes began to appear such as that of V Cornil and Suchard ("Note sur le siège des parasites de la lèpre" Bull et mém Soc méd d hôp 18 151 1881) who describe the same intracellular appearance as had Neisser and of V Cornil ("Second note sur le siège des bactéries de la lèpre et sur les lésions des organes dans cette malade" *ibid* p 155) who discusses the histological appearance of the lesions but adds little if anything, to Neisser's description He found as had Neisser that "in most fibrous tissue the bacteria throw out long filaments in the interstices of the fibers the fixed cells of the fibrous tissue being little altered or normal but there results often a sclerosis a thickening of these fibrous tissues"

From this point on the confirmatory studies on the presence of the bacilli in

leprosy are too numerous to quote They are referred to in detail in McKinley's review (Ref 4)

6 HANSEN G Armauer Studien uber Bacillus leprae Virchows Arch. f path Anat 90 542 1882

From the very discovery of the bacillus several questions were under debate (1) whether the organism was cultivatable (2) whether it could be found in the blood and (3) whether the disease could be transmitted by it to animals Neisser (Ref 5) thought that perhaps he had transmitted the disease to dogs although he stated later (Ref 7) "The result of all experiments to date is Leprosy has thus far not been produced in animals" He also thought that he had cultivated the bacillus H Kobner ("Uebertragungsversuche von Lepra auf Thiere Virchows Arch f path Anat 88 282 1882) tried systematically to transmit the disease to monkeys guinea pigs mice rabbits pigeons eels and frogs always with negative results Hansen in the above paper also failed to produce lepra in a monkey and could not find bacilli in the blood Hansen found bacilli readily in the nodular form of leprosy but not in the anesthetic form He thought however that spore formation obviously takes place in the human body"

In summary all this brings out how difficult these matters were to settle with early inadequate methods Evidently most observers *expected* the bacilli to grow and to be found in the blood and to produce lesions in animals

7 NEISSER A Histologische und bacteriologische Leprauntersuchungen Virchows Arch f path Anat 103 355 1886

P G Unna, the great German dermatologist (Leprastudien Zur Histologie der leprosen Haut" Monatshefte f prakt Dermatol. 1885 Erganzungsheft p 34 and "Die Leprabacillen in ihrem Verhaltnis zur Hautgewebe in *Dermatologische Studien* [Hamburg and Leipzig Leopold Voss 1886] 1 1) in elaborate studies challenged the view of Hansen and of Neisser that leprosy bacilli occurred intracellularly he thought that for the most part they lay without the cells in the lymph spaces This work stimulated Neisser to retort in this long paper in which he sustained his thesis and added other conclusions such as his inability to transmit lepra to animals and the fact that while contagion was possible the probability was slight He still insisted on spores and believed that multiplication outside the body was improbable At any rate man is to be regarded as the chief carrier of the leprosy virus and therefore one should not protest so emphatically in the name of humanity against his isolation Hansen ("Die Lage der Leprabacillen" Virchows Arch f path Anat 103 388 1886) joined shoulders with Neisser to support the intracellular position of the bacilli After all he said one can answer this question only by seeing and "Neisser and I have pictured cells fresh and stained in which we have seen the bacilli"(!) K Touton ("Zur Topographie der Bacillen in der Leprahaut" Virchows Arch f path Anat, 104 381 1886) also took sides with Hansen and Neisser

8 NEISSER A Der Aussatz Lepra *in* H von Ziemssen Handbuch der speciellen Pathologie und Therapie Vol 14, Part I Handbuch der Hautkrankheiten p 620 Leipzig 1883

A systematic article by a great authority on the disease giving its contemporary status Neisser following Danielssen and Boeck (Ref 1) and Virchow (Ref 3) still divided the cases sharply into Lepra tuberculosa and Lepra nervorum It is of interest that in most of the older discussions leprosy was placed in the category of skin diseases

9 [Editorial] The inoculation of a condemned criminal M Rec 29:449 1886

An account is given of the inoculation in Hawaii of a condemned criminal "Finally by permission of the Privy Council Dr Arning was allowed to make an inoculation upon the condemned criminal Keanu whose sentence was commuted to imprisonment for life an inoculation was made of leprous matter in the convict s arm Bacilli were found in the sore or the scar until fourteen months later but no constitutional symptoms were observed We regret to learn that owing to difficulties with the Health Board Dr Arning s work will probably be discontinued" We have been unable to see Arning s own report (referred to by Porritt and Olsen) If correct this is a most important observation which fits in with the prevailing view that leprosy is transmitted with great difficulty The case is questioned by Rogers and Muir (*op cit* p 89) who say that the subject may have contracted his subsequently developing disease [leprosy] through contact with two infected relatives"

R J Porritt and R E Olsen ("Two simultaneous cases of leprosy developing in tattoos Am J Path 23 805 1947) reviewed the literature on transmission by human inoculation and felt that the matter was still in doubt until their observation of two United States Marines who were tattooed successively by the same man on the same day Both developed maculo-anesthetic leprosy in the tattoos about 2 years later "These two cases provide strong evidence for the spread of leprosy by inoculation"

Interesting material on human inoculations is also to be found in the paper by A A St Mouritz "Human inoculation experiments in Hawaii including notes on those of Arning and of Fitch Condensed arranged and annotated by H W Wade" Internat J Leprosy **19** 203 1951

10 HANSEN G Armauer and LOOFT Carl Leprosy in its clinical and pathological aspects Translated by Norman Walker M D F R C P Bristol John Wright & Co 1895

This book is of special interest and importance because in it Hansen summarizes his mature views on leprosy formulated after many years of study of the disease

The introductory chapter deals with the important question of classification The authors make some criticism of Danielssen and Boeck s "nodular and anesthetic" forms and suggest that the terms Lepra tuberosa" (tuberculosa) and Lepra maculo-anesthetica" be used because sooner or later both nodules macules and anesthesia are present The matter of classification has perhaps been needlessly overstressed in the literature it is thoroughly discussed by Arnold (*op cit* pp 17 ff) and by Chaussinand (*op cit* p 185) who presents the problem in the form of an elaborate table

There next follow thorough descriptions of the clinical features with discus

sion of the pathological changes As to prognosis Hansen and Looft state that both forms of leprosy may recover although "patients rarely live more than eight or nine years after the definite outbreak of the disease" (p 85) The chapter on etiology is especially important The writers defend the view that the disease is acquired by contagion and not by heredity as most workers thought at the time "*It is well known that the Belgian Father Damien became a leper in the Sandwich Islands If the Father was of pure Belgian ancestry and his disease was caused by latent hereditary bacilli* then these bacilli must have been at least several hundred years old unless one assumes that one of his nearer ancestors had had connection with a leper, and that in this way the Father had acquired his bacilli Against this in the explanation that the Father who tended the lepers on Molokai with self sacrificing love was through some want of care or caution infected as he went in and out among the lepers The choice between the two explanations does not appear to us a difficult one (p 93) (see also Ref 13) "That leprosy is really contagious is primarily evident from its nature as a bacillary disease Unfortunately all attempts to inoculate animals have failed" (p 95) "How leprosy is caught we do not know, but we think it is probably by inoculation (p 102) Under treatment, the usual mélange of medicine—mader cashew nut oil Gurjun oil chaulmoogra phosphorus arsenic ichthyol carbolic acid creasote [*sic*] mercury iodide tuberculin and many others are mentioned However the writers were not deluded by false claims "The results of the treatment are nothing to boast of but they show that leprosy at its commencement can be cured In our opinion this is true but with the reservation that the cure is not due to treatment but is the natural development of the disease" (p 123) "As we are then, in our opinion unable to destroy the bacilli with remedies either internal or external it only remains to us to prevent infection and that can only be attained by isolation of those affected

11 BABES Victor Die Lepra Vienna Alfred Holder 1901
This monograph of some three hundred and fifty pages was the standard reference book on leprosy at the turn of the century Leprosy was no longer classified as a skin disease and the differentiation between "nodular" and nerve leprosy was less sharply drawn Every feature of the disease is fully discussed and the work is well illustrated There is a comprehensive bibliography

12 JEANSELME Ed La Lèpre Paris G Doin 1934
This handsome folio volume of some seven hundred pages stands out as a landmark in the literature on leprosy Well printed on fine paper and beautifully illustrated the book is a tribute to the printer s art as well as to the scientist s efforts Of special interest is the excellent historical introduction as well as the section on prophylaxis and leprosaria with its many illustrations Every phase of the disease is discussed documented and illustrated

13 AYCOCK W L Familial susceptibility as a factor in the propagation of leprosy in North America, Internat J Leprosy 8 137 1940
Danielssen and Boeck (Ref 1) strongly emphasized the role of heredity in the etiology of leprosy and even after the discovery of the bacillus heredity and

contagion have both had their adherents Aycock a careful epidemiologist brings evidence that heredity may play an important role bv studying the occurrence of leprosy in certain family stocks regardless of contact He concludes "Collected studies covering several generations of family lines in which leprosy continues to occur in several localized areas indicate that hereditary susceptibility is a major factor in the propagation of leprosy on the North American continent Aycock ("Familial susceptibility to leprosy" Am J M Sc 201:450 1941) also gives a comprehensive review of the literature on the subject which leads him to the same conclusion

14 FAGET G H POGGE R C JOHANSEN F A DINAN J F PREJEAN B M and ECCLES C G The promin treatment of leprosy a progress report Pub Health Rep 58:1729 1943

A new era in the treatment of leprosy began with the introduction of the sulfone derivatives in 1941 although their use spread slowly and only an occasional title is found in the *Index medicus* until 1946 Many more papers were written for example on the use of diphtheria toxoid in leprosy W H Feldman H C Hinshaw and H E Moses ("The effect of promin [sodium salt of P P'-diamino diphenyl sulfone N N -dextrose sulfonate] on experimental tuberculosis a preliminary report" Proc Staff Meet Mayo Clin 15 695 1940) tried the drug in experimental tuberculosis and concluded "The results of this experiment support the possible effectiveness of promin in experimental tuberculosis in guinea pigs As a result of this observation the drug was deemed worthy of trial in leprosy Faget and his associates began their studies at the National Leprosarium at Carrville Louisiana in 1941 The drug was given by mouth to a series of ten patients Toxic reactions led to a change to the intravenous route bv which 5 gm nearly every day for long periods was well tolerated A slowly developing anemia is the major toxic reaction A number of case reports are given of unselected patients who received the drug for at least 12 months "Promin appears capable of inhibiting the progress of leprosy in a considerable percentage of cases As yet no case of leprosy has become arrested under its influence It is not claimed that promin is a specific for leprosy Later Faget and Pogge ("The therapeutic effect of promin in leprosy" Pub Health Rep 60 1165 1945) reported further on results of treatment with promin "The present study shows that the improvements observed in the earlier report continue to occur and in a larger percentage of cases than previously reported

Its action is slow and improvements usually become manifest only after 6 or more months of treatment Faget and Pogge point out that from the nature of the case apparent improvement may be due to "psychological responses of patients" or to spontaneous variations in the disease However the photographs which they give of patients with nodular leprosy before and after treatment are really impressive

15 FAGET G H and POGGE R C Treatment of leprosy with diasone a preliminary report New Orleans M & S J 98 145 1945

Diaminodiphenylsulfone has yielded various derivatives which have been tried in leprosy One of these is diasone the disodium formaldehyde sylfoxylate It has the advantage of being usable when given by mouth Faget and Pogge gave

the drug a careful trial in forty seven cases of which only three showed any advance of the disease under treatment The toxic reactions were relatively mild on an average dose of 1 gm daily

The study of various sulfone derivatives has progressed rapidly since these early studies but as yet with no final evaluation Good brief summaries with references of the whole subject of the sulfones in leprosy may be found in the addendum to the third printing of Rogers and Muir (*op cit*) (1951) in H L Arnold s book (*op cit* p 8) and in Chaussinand (*op cit* pp 233 ff) who says (1955) "The published results [of Faget Ref 14] have been confirmed by leprologists all over the world and at present the sulfones are considered the therapy of choice Chaussinand s photographs of patients before and after treatment with D D S (4 4 diamino diphenylsulfone) are very impressive

16 FAGET G H and ERICKSON P T Use of streptomycin in the treatment of leprosy Internat J Leprosy, **15** 146 1947

It was inevitable that any drug useful in tuberculosis should be tried in leprosy Faget and Erickson found that streptomycin "produced encouraging results" but in the large and continuing dosage which was necessary toxic effects were too severe to allow it to be the treatment of choice in leprosy However streptomycin seemed to be useful in the local treatment of chronic leprous ulcerations Erickson (The status of streptomycin and dihydrostreptomycin in the treatment of leprosy Internat J Leprosy 19 1 1951) later reported further observations and stated that "clinical improvement has been almost universal and sustained Again the toxic effects of prolonged therapy were prohibitive but he enumerated various situations in which only short term therapy is necessary —as for example for aborting attacks of acute leprous iridocyclitis—and in which streptomycin may be useful

17 WADE H W Origin of the lepromin test Internat J Leprosy **19** 221 1951

The lepromin test a term coined by P Bargeher ("Kunstliche lepraspecifische Allergie und active Immunisierung gegen Lepra" Ztschr f Immunitatsforsch u exper Therap 49 346 1926) a skin test performed with suspensions of lepromatous material has been much discussed in the literature although like so many facets of leprosy there are disputes as to its significance technique and indeed its discovery Wade carefully analyzes the literature with reference to priority "It has been suggested that the record should be put straight as to when the test which is universally known by Mitsuda s name was first introduced and to whom credit should be given for its inception An attempt to [sic] this is made here" Fumio Hayashi ("Mitsuda s skin reaction in leprosy" Internat J Leprosy 1 31 1933) is much quoted as an early student of the test. In this somewhat dogmatic article Hayashi gives the results of years of work "The intracutaneous injection of leprosy bacilli produces no reaction in patients who have reached the nodular state with unlimited proliferation of the bacilli The positive reaction appears only in normal individuals resistant to leprosy and in lepers in the neuro macular stage in which a certain degree of resistance is to be presumed

DIPHTHERIA

Anatoxin	Ref 22
Antibiotics in diphtheria	Ref 24
Antitoxin	Refs 14 17 20
Bacteriology	Refs 8 10 12 23
Carriers	Refs 10 12 18 24
Experimental diphtheria	Refs 7 10 12
General	Refs 1 4 6 9
Heart in diphtheria	Ref 15
Intubation	Ref 3
"Malignant" diphtheria	Ref 21
Pathology	Refs 11 16
Postdiphtheritic paralyses	Refs 5 6
Schick test	Ref 19
Toxin	Refs 12 13
Tracheotomy	Refs 1 2 9

Section 14

DIPHTHERIA

MODERN discussion of diphtheria begins clearly with Bretonneau he had the genius to recognize the disease as a specific entity and to separate it from the confused welter of sore throats which doctors currently described When we remember however that necrotizing anginas were at the time common complications of scarlet fever and indeed of any severe infection such as smallpox typhoid or typhus and that dirt and neglect of mouth care added further complicating factors it is small wonder that most contemporary authors could do no better than speak of the "putrid" sore throat and the "malignant ulcerous" sore throat as for example John Huxham did in his famous *Essay on Fevers* (London S A Cumberlege 1782) Patients with communicable disorders were crowded together in the filthy wards of fever hospitals and mixed infections were undoubtedly the rule so that when a child had "croup and died from blocking of the air passages it was indeed hard to make an accurate diagnosis

The throat infections of the eighteenth and early nineteenth centuries occurred for the most part in definite epidemics often severe and with a high mortality rate the benign sporadic cases of the late nineteenth century were little seen It was the occurrence in epidemics however which gave the clue to contagion to most serious students of diphtheria Greenhow (Ref 4 p 1) for example makes the following observation "Thus the disease has been repeatedly observed whilst very prevalent in certain districts to pass over others in their immediate vicinity of precisely the same character with respect to soil climate aspect and inhabitants The two districts are divided by the River Stour and the disease prevailed in all the hamlets on the western side of the river while scarcely any cases occurred on the eastern although both are similar in character and appeared to be exposed to the same influences

The much quoted treatises of Francis Home (*An Inquiry into the Nature Cause and Cure of the Croup* [Edinburgh A Kincaid & J Bell 1765]) and of Samuel Bard (*An Enquiry into the Nature Cause and Cure of the Angina suffocativa or Sore Throat Distemper* [New York S Inslee & A Car 1771]) *are too primitive to be included in a modern bibliography Actually one* cannot be certain just what these writers were dealing with Home s cases for example *were found at autopsy to have a tough membrane inside the trachea* "but easily separable as there is always matter behind it " No lesion was found in the throat "There appears from the preceding facts two very different situations of the *Suffocatio stridula* the former more inflammatory and less dangerous the latter less inflammatory and highly dangerous [p 46] I have observed, that the urine which during the inflammatory state is thin had always after the purulent state came on a light ouzy purulent sediment such as people have from matter collected anywhere that has no vent outward" (p 47) Home did *suggest* tracheotomy (p 59) "When the case is desperate may we not try *bronchotomy*? I can see no weighty objection to that operation as the membrane can be so easily got at, and is very loose " Bard described a small outbreak of a disease similar to that reported by Home The tonsils and back parts of the

throat were swollen and covered with white sloughs but the main lesion was in the windpipe "The trachea quite down to its division in the lungs was lined with an inspissated mucus in form of a membrane remarkably tough and firm" Bard stated that the disease was evidently infectious (p 19) but this means little since "all infection must be owing to something received into the body this therefore whatever it is being drawn in by the breath of a healthy child irritates the glands of the fauces and trachea as it passes by them and brings about a change in their secretions In truth the throat altho frequently affected is not the seat of the disease and many have died where that has been entirely free from complaint" (p 31) In a word both Home and Bard were definitely of the eighteenth century any remark which suggests a modern outlook is promptly modified by a meaningless statement based on Galenic ideas Both writers strongly influenced current ideas on sore throats Home by implying that croup was a special disease held back understanding of diphtheria for fifty years until Bretonneau s observations

Good discussions of the history of diphtheria are to be found in the book by Sanné (Ref 9) in Adolph Baginsky s monograph (*Diphtherie und diphtheritischer Croup* [Vienna Alfred Holder 1899]) in F Loeffler s chapter in *The Bacteriology of Diphtheria* edited by George H F Nuttall and G S Graham Smith (Cambridge Cambridge University Press 1907) and in the monumental treatise on *Diphtheria Its Bacteriology Pathology and Immunology* by F W Andrewes and others (London His Majesty s Stationery Office 1923) Behring s little book (*Die Geschichte der Diphtherie* [Leipzig Georg Thieme 1893]) deals especially with the history of immunization in diphtheria August Hirsch in his *Handbuch der historisch geographischen Pathologie* (2d ed Stuttgart Ferdinand Enke 1886) 3 43 under the title of "Angina maligna" gives a comprehensive list of epidemic outbreaks of diphtheria (English translation by Charles Creighton [London New Sydenham Society 1886] 3 66 ff)

As to bibliographies the list of some three thousand titles in Andrewes *et al* (*loc cit*) gives everything of importance up to 1923 The account of the *Corynebacterium diphtheriae* and diphtheroid organisms by R Tanner Hewlett and W Bullock in *A System of Bacteriology in Relation to Medicine* (London His Majesty s Stationery Office 1930) 5 67 is precise but thorough The works of Sanné (Ref 9) and Baginsky (*loc cit*) give classical general accounts of diphtheria among modern briefer but excellent articles are those of J Howard Mueller ("The diphtheria bacilli and the diphtheroids in René J Dubos [ed] *Bacterial and Mycotic Infections of Man* [Philadelphia J B Lippincott Co 1952] p 222) and of F S Cheever ("Diphtheria in R L Cecil and R F Loeb *A Textbook of Medicine* [Philadelphia W B Saunders & Co 1955])

Innumerable books and treatises which cannot be listed here have been written on the subject of diphtheria

1 BRETONNEAU P[ierre] Des inflammations spéciales du tissu muqueux, et en particulier de la diphthérite ou inflammation pelliculaire connue sous le nom de croup d angine maligne d angine gangreneuse etc Paris Crevot 1826 (English translation Memoirs on diphtheria etc. selected and translated by Robert Hunter Semple London New Sydenham Society 1859)

Bretonneau's great book is a collection of four "memoirs" some of which had already been read at the Paris Academy. His chief contribution was his insistence on the identity of syndromes which were regarded as different diseases by Home (*loc cit*) and others—namely diphtheria, malignant angina and "croup." "The gist of the work tends to prove that many lesions of the mucous membranes have been confused while the nuances of one affection have often been taken for different diseases [p 9] . . . The exudation which accompanies them presents remarkable differences, sometimes it is serous, sometimes it is mucoid, sometimes it is white and of a cheesy consistency, sometimes it is a membranous substance intimately adherent [p 10] . . . I undertake to prove by the witness of facts that the scorbutic gangrene of the gums, the croup and the angina maligna are one and the same sort of inflammation" (p 10).

But to this reviewer at least Bretonneau's book is disappointing. Having stated his great and fundamental thesis, the material with which he sustains it is confused and rambling. He leans heavily on opinions and quotations from authors back to the sixteenth century. His case reports are often obscure and not clearly appropriate. There is a long section on mercurial therapy. The fourth memoir includes translations of the work of Ghisi, Samuel Bard, Nola and others. In the additions to the second memoir one finds an interesting section on tracheotomy in which is presented the case of Élisabeth de Puysegur, the daughter of his friend. The operation on this child is described in minute detail.

2. TROUSSEAU, A. Mémoire sur un cas de trachéotomie pratiquée dans la période extrême de croup. *J des connaissances méd chir*, 1 5 41, 1833.

Sanné (Ref 9, p 463) gives Trousseau credit for popularizing tracheotomy in diphtheria. However, the procedure has a stormy history. Home (*loc cit*) advised incision of the trachea as a last resort when the patient with croup was suffocating, but he did not himself perform the operation. Apparently one of the first successfully to execute a tracheotomy was John Andrée, a London surgeon, in 1782. Interestingly enough, his account of the procedure is given secondhand by J R Farre (Appendix to the paper on cynanche laryngea, M Chir Tr, 3 323, 1812) who states: "The above interesting report seems to be deficient only in the particulars of the operation, and these, through the kindness of Mr Astley Cooper, I have obtained. They are given in the words of Mr Andrée." The operation is described: "The respiration was immediately relieved, and the child recovered." Thomas Chevalier ("Account of a case of croup in which the operation of bronchotomy was successfully performed," M Chir Tr, 6 151, 1815) tells of a seven-year-old boy: "No chance of his recovery now seemed to remain, unless it were by opening the trachea, and I was applied to for this purpose. I exposed the trachea . . . and divided two of the cartilaginous rings vertically, cutting afterwards transversely in the interstice between them. Bloody material gushed forth, the child was able to breathe and recovered." But all were not so lucky, there were more failures than successes, and bitter arguments arose as to the advisability of the procedure. Bretonneau (Ref 1) argued strongly in favor of tracheotomy and after two failures had the good fortune in 1825 to save the daughter of his friend, the Count de Puységur. Trousseau, however, gives with all his brilliance a minute description of the case of a six and a half year old child. The disease picture

of the child threatened with suffocation is painted with terrifying vividness "The child almost breathing his last let himself be placed on a dining room table With a burned match I traced on his neck a line so that my bistoury should not go astray" The operation is then described The child had a stormy time there was evidently wound infection Twelve days after operation the cannula was removed he breathed through the larynx and three days later the wound in the neck was healed

Trousseau knew of twenty-one instances in which tracheotomy was practiced seven patients were saved—a good record as all were moribund when the operation was performed "The operation is easy" whereupon he describes the whole procedure in minute detail Henri Roget ("Premier exemple de croup guéri à l'hôpital par la trachéotomie" Bull et mém Soc méd d hôp de Paris 4 209 1858) after many years gave the story of the first case successfully operated on in the Hôpital des Enfants By 1839 Gendron ("Nouvelles considérations sur l angine maligne l angine couenneuse terminée en croup et sur la trachéotomie" Bull Acad de méd Paris 3:908 1839) in a report to the academy advised that tracheotomy not be reserved as a last resort but practiced early the discussion in which ten authorities—including such men as Velpeau Baudelocque Blandin and Roux—joined is full of interest

3 BOUCHUT E D une nouvelle méthode de traitement du croup par le tubage du larynx Bull Acad de méd Paris 23 1160 1857–58

Bouchut seems to have first conceived the idea of intubation for croup "Children with this disease die either of asphyxia or diphtheritic poisoning or of pneumonia Doctors have found nothing better to do when asphyxia is imminent than to open the passages to the air by tracheotomy M Bouchut thinks (he has already done it twice) that one could replace this difficult and dangerous operation which gives a mortality of 80–90 per 100 by a new procedure not bloody and free of all danger no sooner thought of than done it is intubation of the glottis" The instruments and procedure are described, and two cases are reported The academy appointed a committee consisting of MM Blache Nélaton and Trousseau with Trousseau as spokesman to investigate Bouchut s claims (Du tubage de la glotte et de la trachéotomie Bull Acad de méd Paris 24 99 137 214 1858–59) Trousseau in a long report was so antagonistic to the procedure that it fell into disuse until Joseph O Dwyer rediscovered it apparently independently (Intubation of the larynx," New York M J 42 145 1885) O'Dwyer devised a new instrument for inserting and withdrawing the tube which is pictured in his article and he later reported many successful results with the procedure (Analysis of fifty cases of croup treated by intubation of the larynx" *ibid* 47:33 1888) A series of excellent *photographs illustrating the course of the operation is given by* Baginsky (*op cit* pp 340 ff)

4 GREENHOW Edward Headlam On diphtheria London John W Parker & Sons 1860

Greenhow s book summarizes very well the position of diphtheria in the mid nineteenth century While Greenhow s description (p 5) clearly includes diphtheria it is probable that other types of sore throat, especially scarlet fever are to some extent confused with it "Diphtheria is sometimes preceded and

usually accompanied by fever There is often a stiffness of the neck at the commencement of an attack and usually *more or less swelling* and tenderness of the glands at the angles of the lower jaw The tonsils are commonly swollen and together with the immediately contiguous parts of the mucous surface more or less *inflamed* Sometimes the swelling and inflammation subside without further local mischief at others the inflamed surface presents from an early stage of the disease whitish *specks or patches* on a continuous covering of a membraniform aspect which usually soon becomes opaque and in some cases assumes the appearance of wet parchment or chamois leather This membranous concretion varies in colour from being slightly opaque to white ash colour buff or brownish and in rarer instances to a blackish tint

When the false membrane has been artificially removed it is apt to be renewed The severity of the disease *is commonly* in proportion to the continuity and density of the exudation If the patches are small and remain distinct the case ordinarily runs a favourable course [are these cases of follicular tonsillitis?] If they rapidly coalesce if the membrane becomes thick and especially if it assumes a brownish or blackish colour danger is imminent. The surface of the mucous membrane around the exudation is red and vascular and so tender that in severe cases it bleeds on the slightest touch The throat is in general the primary seat of the disease but the inflammation is apt to spread along continuous mucous surfaces and thus to extend upwards into the nares and the conjunctiva down the pharynx into the oesophagus through the glottis into the larynx trachea and downwards into the bronchial tubes or forward on to the buccal mucous membrane the gums and lips Wounds and excoriations of the skin are during an epidemic liable to undergo the same process of exudation which coagulating forms a false membrane analogous to that on the tonsils and throat After a time the false membrane is thrown off either entire so as to represent a mould of the parts it covered or, which is more usual comes away in shreds or flakes intermingled with mucus

Occasionally sloughing takes place beneath the exudation The power of swallowing is sometimes so impaired that there has been difficulty in sustaining life during convalescence and liquids are apt even after a comparatively slight attack to be regurgitated through the nostrils Extreme anemia impairment of vision a peculiar form of paraplegia weakness of the hands and arms numbness tenderness of the limbs tingling wandering pains and more rarely nervous sequelae of a hemiplegic character are in the order here written, ulterior consequences of diphtheria " Greenhow observed sudden death perhaps of cardiac origin as a frequent mode of termination It would be hard to find a more exact and precise description today

Greenhow had trouble in accurately diagnosing many sporadic cases of sore throat but he was sure that scarlet fever and diphtheria were totally distinct diseases and that an attack of one did not protect against the other He did not however believe that diphtheria was contagious as Bretonneau insisted "Facts already related have in my opinion clearly shown that diphtheria is of indigenous origin and capable of being generated anew (p 138)

Greenhow showed an amazing conservatism as to therapy in an era when medicines were wildly used As to local treatment of the throat he said I am sure much mischief has been produced by its indiscriminate use especially by the frequent tearing away of the exudation by probangs or similar con

trivances for the application of nitrate of silver or of strong caustic solutions

I very soon discontinued this rough local medication to the tender and already enfeebled mucous membrane In the first place the application can but rarely extend to the entire diseased surface and in the next the subjacent tissues are so deeply involved in cases of really malignant diphtheria that any application to the mucous membrane could apparently exercise no beneficial influence upon the disease" (p 263) He advised mild cleansing methods such as gargles of tepid water Upbuilding safeguarding and avoidance of bleeding are emphasized He had no experience with tracheotomy which had been in this country almost always unsuccessful (p 270) although he thought that it might be lifesaving in a certain type of case in which the air passages were plugged with membrane "Time is the most important agent towards recovery from the several forms of nervous affection which follow diphtheria" (p 273)

5 CHARCOT and VULPIAN Note sur l'état des muscles et des nerfs du voile du palais dans un cas d'angine diphthéritique Compt rend Soc de biol 4:173 1863 (1862)

Postdiphtheritic paralyses are described in practically every general discussion of diphtheria (Refs 2 4 9) from Bard on The frequency varies J O Rolleston ("Diphtheritic paralysis" Arch Pediat 30 335 1913) among twenty three hundred personal cases found an incidence of 20 7 per cent In very severe cases the incidence was 48 1 per cent as against 0 0 per cent in mild cases There is much more interesting statistical material in this article "The outlook in diphtheritic paralyses may be said to depend upon the age of the patient the date of onset and the situation of the paralysis The older the patient the better the prognosis Cardiac pharyngeal and diaphragmatic palsies are the only kind which need cause anxiety

There has been great discussion as to the nature of the lesion since Charcot and Vulpian in their famous case described the muscle fibers of the palate as appearing normal whereas "the nerves of the soft palate showed remarkable alterations Some of the nerve fibers are represented by tubes entirely void of medullary substance The writers continue with more details of the nerve lesions P Meyer later in his important review of the subject with bibliography ("Anatomische Untersuchungen uber diphtheritische Lahmung Virchows Archiv f path Anat 85 181 1881) says "It turns out that the peripheral nerves are the seat of unequivocal and widespread changes" A detailed description of these lesions follows F R M Walshe (On the pathogenesis of diphtheritic paralysis Quart J Med 11 191 1918) studied the subject extensively and concluded that "diphtheritic paralysis at any rate in cranial nerve involvement is an ascending infection of the central nervous system the toxin elaborated in the membrane passing up to the medulla in the perineural lymph channels of the cranial nerves innervating the tonsils and fauces This thesis is sustained in further papers (*ibid* 12 14 32 1919) The whole subject is reviewed by Andrewes *et al* (*op cit* pp 223 ff)

6 TROUSSEAU A Clinique médicale de l'Hôtel Dieu de Paris Paris J B Baillière et fils 1865 2d ed Diphtherie (Mal egyptiaque) 1 334

Trousseau the master clinician covers the subject in eight lectures We shall not quote in detail his admirable description of the various forms of the disease. He differed from Greenhow on the value of local treatment and with reference to a case of malignant diphtheria he tells how "I immediately instituted the treatment which alone offered some chance of success I cauterized the involved parts vigorously with a 20 per cent solution of silver nitrate and then insufflated powdered alum That evening and the next day the cauterizations were repeated with a saturated solution of copper sulfate In the intervals one gave insufflations alternately of alum and tannic acid In spite of this I insisted on their feeding the child with soup chocolate and coffee at the same time I ordered a quinine preparation" Four days later the child was no better and it finally died in syncope "although the local appearance was improved of the diphtheritic poison which had infected it This is a good example of standard therapy of the day

Then follows a lecture on the various localizations of diphtheria—palpebral, cutaneous vulvar vaginal anal and preputial Trousseau points out that they are all the same disease "Diphtheria is, then par excellence a specific disease whose different manifestations local and general only constitute variations within the species which are all to be traced to the action of a unique morbid principle a special virus it is in a word a pestilential disease [*une maladie pestilentielle*] Like all specific diseases it is contagious and perhaps inoculable although the experiments designed to give a vigorous demonstration of the latter have been fruitless" He quotes a good deal of anecdotal material on inoculability but is quite certain that the disease is contagious although sometimes its mode of transfer from one locality to another is not easy to grasp

The next lecture deals comprehensively with postdiphtheritic paralyses which he says have been overlooked by many recent writers although "their existence has been categorically demonstrated by three authors of the middle and end of the last century Ghisi Chomel and Samuel Bard" Trousseau describes paralysis of the palate of the sense organs of the limbs and of the muscles of respiration and deglutition He discusses the nature of these paralyses He did not believe that they depended on an anatomical lesion but thought that they were analogous to what we see in certain cachexias" and were an effect of the intoxication of the body economy by the poison of the disease In the lecture on treatment Trousseau reverts to a host of Galenic remedies but there is an excellent discussion of the indications for and the technique of tracheotomy

7 OERTEL [M] Experimentelle Untersuchungen uber Diphtherie Deutsches Arch f klin Med 8 242 1871

Although attempts had early been made to transmit diphtheria to animals a surgeon Trendelenburg ("Ueber die Contagiositat und localer Natur der Diphtheritis" Arch f klin Chir 10 720 1869) seems to have been the first to have any real success He performed tracheotomy on rabbits and introduced tiny particles of diphtheritic false membrane The animals died in a few days and at autopsy had lesions resembling diphtheria Oertel went a step further and in an elaborate investigation not only produced diphtheria in rabbits but passed it from animal to animal These observations were of course not con

firmed bacteriologically but they seem plausible At any rate the authors were convinced that the disease was due to a living agent and was communicable Oertel thought of the disease as at first localized and then spreading throughout the body

8 KLEBS E Beitrage zur Kenntnis der Micrococcen Arch f exper Path u Pharmakol 1 31 1873

Credit for discovery of the causal organism of diphtheria is usually given to Klebs and to Loeffler (Klebs Loeffler bacillus) Klebs s first paper however in the very early days of bacteriology deals with the crudest sort of attempts at cultures A careful reading of the paper with reference to the bits of membrane from the throats of "diphtheritis" patients as well as a scrutiny of the illustrative plates does not give the slightest hint that Klebs saw or isolated the bacilli of diphtheria Klebs was an energetic imaginative man always a step ahead of the field and almost always wrong as for example in his claims of isolating the causal organisms of typhoid fever and of pneumonia Nor do further instalments of these studies (*ibid* 3 305 1875 4 107 207 409 1875) give the slightest hint that Klebs dealt with *Corynebacterium diphtheriae* Indeed aside from his enthusiasm and energy all this material may be pretty much written off as of historical interest only in connection with "cobacteriology" Indeed Klebs like Virchow (Ref 11) was badly confused and tried to differentiate cases of "croup" and of "diphtheria" He did not believe that diphtheria was a specific disease

Finally in a symposium on diphtheria (Verhandl des Congr f inn Med 2d Congr [Wiesbaden J F Bergmann 1883] III Sitzung "Ueber Diphtherie" p 134) Klebs gave his matured views as follows He now divided cases of diphtheria into two forms one caused by a micrococcus and another associated with the presence of "threadlike structures" "By the greatest magnification it appears that very short and narrow rods are regularly seen imbedded in the superficial layer of the false membrane One can convince himself that groups of rods always lie in the cells As to the form of these rods they are uniform and hardly reach the size of a tubercle bacillus A considerable proportion is spore-bearing and indeed there are always two terminal spores in each rod As the membrane dries spores increase notably so that one finds that many rods contain four spores" In summary then as to the bacillary forms of diphtheritis one finds "the constant presence of a particular form of bacillus on the diseased mucous membrane which first develops in the epithelial cells and elicits fibrinous exudate as a result of a peculiar vascular lesion"

What was it that Klebs was dealing with? We must leave it to the reader to decide Loeffler himself (Ref 10) conceded the fact that Klebs probably saw the specific bacteria which he (Loeffler) later isolated However at best Klebs s demonstration of a causal organism was crude and incomplete

9 SANNE A Traité de la diphthérie Paris G Masson 1877

This volume of 654 pages is the outstanding treatise to date on diphtheria It opens with a valuable and well-documented chapter on the history of the disease and then goes on to the pathology which is discussed in minute detail Next come sections on clinical symptoms pertaining to all forms of diphtheria the pages on diphtheritic paralyses are especially detailed and well documented

Trousseau the master clinician covers the subject in eight lectures We shall not quote in detail his admirable description of the various forms of the disease He differed from Greenhow on the value of local treatment and with reference to a case of malignant diphtheria he tells how "I immediately instituted the treatment which alone offered some chance of success I cauterized the involved parts vigorously with a 20 per cent solution of silver nitrate and then insufflated powdered alum That evening and the next day the cauterizations were repeated with a saturated solution of copper sulfate In the intervals one gave insufflations alternately of alum and tannic acid In spite of this I insisted on their feeding the child with soup chocolate and coffee at the same time I ordered a quinine preparation Four days later the child was no better and it finally died in syncope although the local appearance was improved of the diphtheritic poison which had infected it" This is a good example of standard therapy of the day

Then follows a lecture on the various localizations of diphtheria—palpebral, cutaneous vulvar vaginal anal and preputial Trousseau points out that they are all the same disease Diphtheria is then par excellence a specific disease whose different manifestations local and general only constitute variations within the species which are all to be traced to the action of a unique morbid principle a special virus it is in a word a pestilential disease [*une maladie pestilentielle*] Like all specific diseases it is contagious and perhaps inoculable although the experiments designed to give a vigorous demonstration of the latter have been fruitless He quotes a good deal of anecdotal material on inoculability but is quite certain that the disease is contagious although sometimes its mode of transfer from one locality to another is not easy to grasp

The next lecture deals comprehensively with postdiphtheritic paralyses which he says have been overlooked by many recent writers although "their existence has been categorically demonstrated by three authors of the middle and end of the last century Ghisi Chomel and Samuel Bard" Trousseau describes paralysis of the palate of the sense organs of the limbs and of the muscles of respiration and deglutition He discusses the nature of these paralyses He did not believe that they depended on an anatomical lesion but thought that they were analogous "to what we see in certain cachexias" and were an effect of the intoxication of the body economy by the poison of the disease In the lecture on treatment Trousseau reverts to a host of Galenic remedies but there is an excellent discussion of the indications for and the technique of tracheotomy

7 OERTEL [M] Experimentelle Untersuchungen uber Diphtherie Deutsches Arch f klin Med 8 242 1871

Although attempts had early been made to transmit diphtheria to animals a surgeon Trendelenburg ("Ueber die Contagiositat und localer Natur der Diphtheritis" Arch f klin Chir 10 720 1869) seems to have been the first to have any real success He performed tracheotomy on rabbits and introduced tiny particles of diphtheritic false membrane The animals died in a few days and at autopsy had lesions resembling diphtheria Oertel went a step further and in an elaborate investigation not only produced diphtheria in rabbits but passed it from animal to animal These observations were of course not con

a participation of the kidneys heart and central nervous system Nonetheless the main interest remains centered in the local affection " There follows an interesting critical review of previous work on the nature and cause of diphtheria Loeffler concluded "If we survey this material and ask whether the investigator has fulfilled the modern postulates [for a bacterial cause] the answer is No " Loeffler saw the masses of bacilli which were stained well with methylene blue as well as cocci in sections of false membrane he differentiated the lesions of scarlet fever with their preponderant flora of cocci from the lesions in true diphtheria He pointed out that in throats not the site of an actual diphtheria infection there was no real false membrane but simply exudate which was readily scraped away and that these were coccal infections Similar lesions were found in smallpox typhoid and other infections

But Loeffler's great contribution was the recovery in pure culture of the causal organism He described the technique of isolating the bacilli on various media of which coagulated sheep serum (Loeffler's medium) was best There follows a long series of experiments in which all sorts of small animals were inoculated with cultures Guinea pigs were found highly susceptible with death in 2–5 days There were local hemorrhagic infiltrations pleural effusions brownish lesions in lungs and congestion of kidneys and suprarenals but no organisms were recovered except from the local site of inoculation Rabbits were also susceptible but less so than guinea pigs Finally Loeffler gives a critical analysis of the arguments for and against the bacilli as the specific cause of diphtheria and concludes with admirable conservatism "Strict proof that the rods are the cause of diphtheria has then not been brought" he was thinking in terms of complete fulfilment of Koch's postulates He was disturbed by finding bacilli indistinguishable from the diphtheria rods in the pharynx of a healthy child and opened the question of carriers by saying "It is however conceivable that at a time when many cases of diphtheria are occurring the presumptive cause of the disease could be found in the pharynx of an occasional child without eliciting symptoms of any sort " He also opened the possibility of a soluble toxin "The possibility that the bacilli secrete the virus of diphtheria is not excluded "

Thus Loeffler "skimmed the cream" of diphtheria study in a masterful fashion, and his report will always remain a classic

11 OERTEL, M J Die Pathogenese der epidemischen Diphtherie nach ihrer histologischen Begrundung mit Atlas von 16 chromolithographierten Tafeln Leipzig F C W Vogel, 1887

Although there were already many partial descriptions of the pathological changes in human diphtheria this monograph of Oertel is a landmark of thoroughness After a comprehensive review of the previous literature there are elaborate and detailed descriptions of both gross and microscopic lesions to which is appended an atlas of colored plates Of no less importance is the monograph by W T Councilman F B Mallory and R M Pearce (*A Study of the Bacteriology and Pathology of Two Hundred and Twenty Fatal Cases of Diphtheria* [Boston Privately printed 1901]) to which are appended numerous beautiful photomicrographs and a comprehensive bibliography The changes in every organ are described in meticulous detail The whole subject is reviewed in Andrewes *et al* (*op cit* pp 216 ff) It is of historical interest

Sanné points out that these disturbances are *essentially* postdiphtheritic and occur usually from the eighth to the fifteenth day of convalescence the palate and upper portion of the larynx being most frequently affected (p 152) Their nature seems to be a peripheral neuritis Circulatory collapse is well described (p 148) "The adult may have a feeling of impending death and bids his friends goodbye Respiration is rapid but on auscultation there are no abnormal murmurs The pulse is small irregular and unequal soon it becomes thready it is slowed it rarely exceeds 60–100 beats more often it falls to 50 or 40 beats in one case it did not beat over 26 Here then is pretty clear evidence of heart block Sanné recognized croup as simply a clinical form of diphtheria (p 193) Under diagnosis he clearly differentiated between acute tonsillitis and diphtheria (p 276) There is an interesting discussion of epidemics and their origin "The origin of epidemics of diphtheria can then be explained first by the importation of the causal germs into a healthy locality whether the importer is frankly ill with the disease or whether he brings germs which have long remained latent" Sanné believed that most cases arose by direct contact less often by inoculation but also by the ambient air "This is the method par excellence of epidemic and contagious diseases"—an idea which was so in trenched in medical thinking that it was hard to extirpate it. Writing at the beginning of the bacteriologic era he could say about the nature of the diph theria poison only that the tendency which comes to us from Germany and which consists in giving in pathology a large place to a parasitic element would make of diphtheria a zymotic disease" Under treatment there is given first an interminable list of caustics and "dissolvements" to do away with the false membrane and an equal array of every conceivable drug for internal use Sanne concluded however If the disease was purely local one would find without trouble in this therapeutic arsenal some means of mastering it But some such as the cauterizing agents are dangerous and worse than the disease The others milder are not powerful enough" Most of the remainder of the book is devoted to a 200-page treatise on tracheotomy too long to review but cover ing every aspect of the subject with comprehensive bibliography

10 LOEFFLER Friedrich Untersuchungen uber die Bedeutung der Micro-organismen fur die Entstehung der Diphtherie beim Menschen bei der Taube und beim Kalbe Mitt. a d k Gsndhtsamte 2 421 1884

Loeffler's studies as definitive as those of Klebs (Ref 8) were vague and in complete appeared appropriately in the same volume as Koch's classical paper on the etiology of tuberculosis Loeffler along with Bretonneau Behring and a few others stands out as a giant in the history of diphtheria

Loeffler begins by firmly supporting Bretonneau's claim that diphtheria was a specific infection and a communicable disease an ens morbi like measles and smallpox and not simply a group of symptom complexes caused by various agents While he postulated a bacterial cause he felt that diphtheria differed from the usual infections insofar as the active disease was confined to the surface of the mucous membranes exposed to the air and hence was liable to invasion by all sorts of organisms The problem to Loeffler was to sort out these agents and to isolate from among them the essential cause of diphtheria "In vestigation of the internal organs can naturally not be neglected since several symptoms such as albuminuria sudden collapse late paralysis etc point to

find them with all their virulence in the throats of people who have had the disease but in whom there is no more false membrane and in whom the mucosa is perfectly healthy" Thus Roux and Yersin raised the important question of healthy carriers (*porteurs*) Later they said again "Active diphtheria virus can persist in the mouth for a long time after the disease is cured consequently people who have had diphtheria should not be returned to ordinary life while they are still carriers of the bacillus" Roux and Yersin worked out the guinea pig test for virulence of diphtheria bacilli and pointed out that there was no regular agreement with the severity of the clinical case They designated as pseudo-diphtheria bacilli organisms morphologically and culturally indistinguishable from virulent bacilli but harmless for animals which they obtained from non-diphtheritic sore throats and from the throats of healthy children They found that "virulence" ran parallel to toxin formation and they presented evidence that "attenuated" or "avirulent" strains might regain their virulence

Thus Roux and Yersin opened many important questions and plunged into some of the most perplexing problems of diphtheria Their work was promptly confirmed by various workers such as A. Kolisko and R Paltauf ("Zum Wesen des Croups und der Diphtherie" Wien. klin Wchnschr 2 147 1889)

A full discussion of the production of toxin and of its properties is to be found in Andrewes *et al* (*op cit* pp 101 ff)

13 BRIEGER L and FRAENKEL Carl I Untersuchungen über Bakteriengifte Berl klin Wchnschr 27 241 268 1890

The work of Roux and Yersin (Ref 12) stimulated an immense amount of study on diphtheria toxin Loeffler himself (Der gegenwärtige Stand der Frage nach der Entstehung der Diphtherie" Deutsche med. Wchnschr 16 81 108 1890) took a hand in the problem He stated that he had become convinced that diphtheria was a local infection by the fact that in guinea pigs he was never able to find the bacilli except at the site of inoculation He thought that there might be a soluble toxin and he tried to extract it. He procured some material which gave local pain and edema on injection but did not produce typical paralyses Brieger and Fraenkel made a systematic investigation of bacterial poisons in the course of which they studied bacteria free filtrates of diphtheria bacillus cultures Alcohol precipitates were highly toxic and gave the reactions of a protein hence they named it a "toxalbumen" They measured the great toxicity of the material of which 2-5 mg/kg were sufficient to kill a rabbit The animals also developed typical diphtheritic paralyses This paper really opened the intensive study of the subject and an immense amount of work was subsequently done on the nature of the toxin Modern aspects of the subject are reviewed by Mueller (*op cit* p 226)

14 BEHRING E and KITASATO S Ueber das Zustandekommen der Diphtherie Immunitat und der Tetanus Immunitat bei Thieren Deutsche med. Wchnschr 16 1113 1890

C Fraenkel s ("II Immunisierungsversuche bei Diphtherie" Berl klin Wchnschr 27 123 1890) account of attempts to immunize against diphtheria appeared one day before the classical paper of Behring and Kitasato The story of the question of priority is told in interesting detail in the book by Professor Behring (*Die Geschichte der Diphtherie* [Leipzig Georg Thieme 1893])

that the influential Virchow, who early contested Bretonneau's ideas on purely anatomical grounds and insisted on the essential difference between diphtheria and croup, stuck to his views as late as 1885 (R Virchow, "Croup und Diphtherie," Berl klin Wchnschr 22:129 1885)

12 ROUX E and YERSIN A Contribution à letude de la diphthérie Ann Inst Pasteur 2 629 1888

Roux and Yersin were among those who early confirmed the work of Loeffler and isolated from the false membranes of diphtheria the typical bacteria which they grew in pure culture They also obtained lesions in animals as had been done by Loeffler After the mucous membranes were injured lesions were readily produced "The affection which one causes in rabbits recalls the croup in man The difficulty which the animal has in breathing the noise made by air passing through the obstructed trachea the appearance of the trachea congested and plugged by false membrane the edematous swelling of the tissues and glands of the neck render this resemblance absolutely striking" On subcutaneous injection guinea pigs were specially susceptible and died usually within 36 hours with typical local lesions Roux and Yersin were impressed by the fact that the growth of diphtheria bacilli was confined to the region of inoculation no diphtheria bacilli could be grown from the internal organs But in spite of this the experimental animals often developed paralyses which were regarded as highly specific of diphtheria It was these facts which led the writers deliberately to search for a soluble "poison" developed at the local site of growth and thence absorbed to promote remote mischief

Working with limpid bacteria free filtrates of diphtheria bacillus cultures they produced in rabbits for example dilatation of blood vessels especially in *the suprarenals and kidneys ecchymoses along blood vessels* and pleural effusions as well as muscular paralyses which often became generalized and affected the muscles of respiration They concluded therefore that the bacilli produced a soluble toxin and they raised the question of whether it might be an alkaloid or a diastase Its effect was diminished by heating and by exposure to air "Is it possible to accustom animals to the poison of diphtheria and to produce in them by this means immunity to diphtheria? Thus they raised the question which eventually led to modern methods of immunization

In a second note (*ibid* 3 273 1889) Roux and Yersin summarized their findings as follows "Diphtheria is an intoxication caused by a very active poison formed by the microbe in the local region where it develops We have proved this by showing that in pure cultures of diphtheria bacilli there is a specific chemical substance which introduced under the skin of animals gives them the disease in the absence of a single living organism" The bulk of this paper is devoted to describing the characteristics of the toxin such as its high potency and the fact that it appears harmless when given by mouth Finally they found it difficult to habituate animals to the toxin because of its great potency

In the third memoir of this series (*ibid* 4 385 1890) Roux and Yersin again describe the diagnosis of diphtheria by microscopic examination of bits of false membrane and by isolating the specific bacilli in culture Next they determined how long after clinical recovery bacilli persisted in the throat "Rapid disappearance of diphtheria bacilli is not always the rule one can still

serum for both prevention and treatment was being made commercially Numerous further articles appeared in those years by Behring and his group and others which cannot be enumerated here

The nature and preparation of antitoxin are discussed in detail in Andrewes *et al* (*op cit* pp 126 ff)

15 ROMBERG Ernst Ueber die Erkrankungen des Herzmuskels bei Typhus abdominalis Scharlach und Diphtherie Deutsches Arch f klin Med 48:369 1891

There has long been a clinical impression that the heart may be seriously affected in diphtheria (Ref 4) Romberg a prominent student of the subject critically reviewed the early literature and presented contemporary views His own observations revealed definite changes in the heart muscle especially cellular infiltration and focal degenerative areas Similar findings were described by Baginsky (*op cit* pp 189 ff) who also discussed the clinical features It is very difficult to tell in these older accounts whether the patient was suffering from cardiac failure in the usual sense or from a shocklike state of peripheral origin

The upshot of the large and controversial modern literature on the subject is well summarized by E A Burkhardt, C Eggleston and L W Smith ("Electrocardiographic changes and peripheral nerve palsies in toxic diphtheria" Am J M Sc 195 391 1938) Clinically there may be evidence of gross congestive failure or there may be the syndrome of "peripheral vasomotor shock" such as is seen with cardiac infarction Arrhythmias are of frequent occurrence including A V dissociation T wave changes and conduction defects are the principal electrocardiographic alterations The anatomical changes in the heart muscle are on the whole not striking although patchy areas of degenerated muscle fibers and leukocytic infiltration are seen I Gore ("Myocardial changes in fatal diphtheria" Am J M Sc 215 257 1948) in a careful anatomical study of 221 cases found evidence of myocarditis in 70 per cent He regarded the lesion as a primary toxic myocarditis which culminated in scarring a sequel of the pharmacological effect of toxin If the patient survived however T D Jones and P D White ("The heart after severe diphtheria" Am Heart J 3 190 1927) found no evidence of appreciable chronic effect on the heart, although N H Boyer and L Weinstein (Diphtheritic myocarditis" New England J Med 239 913 1948) believe that when there have been abnormal electrocardiographic patterns recovery is probably associated with loss of muscle substance and is therefore never "complete"

16 WELCH William H and FLEXNER Simon The histological changes in experimental diphtheria Bull Johns Hopkins Hosp 2:107 1891

Although von Babes ("Untersuchungen uber den Diphtheriebacillus und die experimentelle Diphtherie" Virchows Arch f path Anat 119 460 1890) had described the pathological changes in experimental diphtheria in rabbits Welch and Flexner s observations were definitive They discussed first the lesions produced by injection into small animals of living cultures of diphtheria

Actually Fraenkel was confused about the whole subject and his attempts at immunization consisted of injecting both whole cultures treated in various ways and growth products (toxin) His results were indecisive as regards the production of immunity Fraenkel thought that toxic and immunizing substances existed side by side in culture fluids he believed that they could be separated by heating since the toxic material was destroyed at 55 -60 C but even with the remainder he was unable to obtain complete protection The report seems to us of little value and Fraenkel beclouded rather than clarified, the issue The paper of Behring and Kitasato actually dealt mainly with tetanus, but the similarity between the mechanisms of protection in the two diseases was clearly recognized "The immunity of rabbits and mice which have been immunized against tetanus rests on the ability of the cell free fluids of the blood to render harmless the toxic substances which tetanus bacilli produce In these brief words Behring and Kitasato first definitely stated the principle underlying antitoxic immunity [1] They showed furthermore that the antitoxic substances existed in extravascular blood and serum that this property was so stable that it remained effective when serum was injected into another animal and that protective properties of the blood are absent in animals which are not immune to tetanus They predicted that such sera would be useful for the treatment of diphtheria and tetanus in man A week later Behring's paper (Untersuchungen über das Zustandekommen der Diphtherie Immunitat bei Thieren" Deutsche med Wchnschr 16 1145 1890) on diphtheria immunization appeared While he clearly recognized the antitoxic effects of cell free blood serum he did not yet challenge antitoxin by injection of bacteria free toxin except in the case of sterile pleural effusions produced in rabbits by injections of virulent cultures He actually used five different methods of immunization "none of which are applicable to man"

The practical application was slow in developing Von Behring Boer and Kossel ("Zur Behandlung diphtheriekranker Menschen mit Diphtherieheil serum" Deutsche med Wchnschr 19 389 1893) used a serum derived from sheep which they stated was "as harmless for man as a sterilized solution of physiological saline They made a rough titration on guinea pigs and found that 5 cc of this serum protected a 500 gm guinea pig against 0 8 cc of diphtheria "toxin" if given 15 minutes in advance Kossel in the second part of the paper reported clinical results which looked promising but were not yet definitive In another paper von Behring Boer and Kossel (III De Werthbestimmung des Diphtherieheilserums" *ibid* p 415) tell in detail of the preparation and use of their sheep serum In a further instalment von Behring ("IV Ueber sogenannte septische Falle von Diphtherie" *ibid* p 543) tells of saving very acute septic" cases of diphtheria with the serum and finally (von Behring "Die Gewinnung der Blutantitoxin und die Classificierung der Heilbestrebungen bei ansteckenden Krankheiten" *ibid* p 1253) discusses antitoxins in a general way By 1894 (von Behring and Ehrlich III Zur Diphtherieimmunisierungs und Heilungsfrage *ibid* 20:437 1894)

[1] In a footnote Behring and Kitasato say "One may designate these actions against bacterial poisons as antitoxic or antifermentative in contrast to antiseptic and disinfectant, both of which refer to antagonistic action against living infectious material"

more medicine but of a better organization of services"[2] The subject of serum therapy of diphtheria is reviewed in Andrewes *et al* (*op cit* pp 257 ff)

18 LEDINGHAM J C G and ARKWRIGHT J A The carrier problem in infectious diseases New York Longmans Green & Co 1912

Indications of the existence of healthy carriers of diphtheria bacilli were already forthcoming in some of the early work on the disease (Ref 10) Since then a huge literature has sprung up in which convalescent carriers and healthy contact carriers are differentiated Early observations on carriers are authoritatively summarized in the book by Ledingham and Arkwright Much of the work also dealt with the question of the duration of the carrier state especially in convalescence from clinical diphtheria An important paper is that of G H Weaver ("Diphtheria carriers" J A M A 76 832 1921) which contains statistical material derived from a study of five hundred cases of diphtheria Weinstein (Ref 24) reviews the modern literature and points out the disagreement between the figures of various workers He concludes however that the elimination of the carrier state in 3-5 days by adequate dosage of penicillin is statistically valid "A minimum of 240 000 units of penicillin per day for 12 days is suggested for the treatment of the chronic diphtheria carrier state" It is of interest also that H D Wright ("The disappearance of C diphtheriae from diphtheria patients" J Path & Bact 52 129 1941) found that the mitis intermedius and gravis types persisted for different lengths of time after acute infection The matter is further complicated by the question of how many carrier strains are virulent A B Wadsworth has studied this problem ("Virulence of diphtheria bacilli from diphtheria patients and from carriers" J A M A 74 1633 1920) He found that "B diphtheriae from persons who have had diphtheria or from those who through contact become carriers retains its virulence for several months" J C Geiger F L Kelly and W M Bathgate ("Diphtheria carriers" J A M A 66:645 1916) first pointed out the importance of nasal cultures in the detection of carriers and then reported Schick tests which showed that all of a group of contact carriers were immune and hence did not require quarantine none of these individuals developed diphtheria

19 SCHICK B Die Diphtherietoxin Hautreaction des Menschen als Vorprobe der prophylaktischen Diphtherieheilseruminjektion Munchen med Wchnschr 60 2608 1913

Schick ("Kutanreaction bei Impfung mit Diphtherietoxin" Munchen med Wchnschr 55 504 1908) had already studied the effect of injecting minute amounts of diphtheria toxin into the skin He found the reaction specific since mixtures of toxin and antitoxin produced no visible effect He concluded therefore that a positive test indicates absence of antitoxin in the blood—in other words susceptibility He also found that by means of the skin test one could estimate accurately the quantity of antitoxin necessary for cure of a clinical case of diphtheria

[2] In a footnote Roux describes the terrible conditions in the diphtheria wards—crowding no ventilation, all sorts of infections herded together It is above all in winter when the pavilion is full when the windows stay closed that bronchopneumonia becomes terrible" etc

bacilli and described the histological changes in great detail in a second paper ("The histological lesions produced by the tox albumen of diphtheria" Bull Johns Hopkins Hosp, 3 17 1892) they compared these with the changes following injection of culture filtrates (toxin) It may be considered as established now that the toxic products and not the bacilli themselves invade the tissues in diphtheria This fact would at once suggest that the general lesions were the effects of the soluble poison diffused through the body Hence it was desirable to demonstrate this assumption experimentally and it is not unimportant to know that the lesions in the tissues produced by the bacilli and the toxic principle on the one hand and the toxic principle alone on the other are in perfect correspondence with each other and moreover it would seem not to be superfluous to emphasize the occurrence of definite focal lesions in the tissues of the body produced by a soluble poison circulating in the blood"

Details of the lesions in every sort of animal are given in Andrewes et al (*op cit* pp 170 ff)

17 ROUX E and MARTIN L Contribution à l'étude de la diphtérie (*sérum thérapie*) Ann Inst Pasteur 8 609 1894

Roux and Martin's precise and lucid style is a relief after the ponderous and turgid writings of von Behring and his associates First is given a brief and clear description of how to obtain diphtheria toxin by filtering old cultures of virulent strains of bacilli In order to get larger quantities of antitoxin Roux and Martin immunized horses The horses which we immunized are not valuable animals [*animaux de prix*] but cab horses [*des chevaux de fiacre*] six to nine years old" These horses were desirable because very tolerant of toxin horse No 1 for example in 2 months and 20 days received 800 cc of toxin After a few days the serum of these horses was already antitoxic When such serum was added to diphtheria toxin it became harmless both in test tube and in vivo Antitoxin rendered an animal immune immediately but for a short time only several days or at the most a few weeks Roux and Martin emphasized the quantitative relations of toxin and antitoxin under various circumstances the antitoxin kept well in the dark and cold Next are reported prophylactic and curative injections in guinea pigs and rabbits they describe the subsidence of edema and the melting away of the false membrane The treatment of children is reserved for another paper (E Roux L Martin and A Chaillou Trois cent cas de diphtérie traités par le serum antidiphtenque" Ann Inst Pasteur 8 640 1894) The three hundred children treated had a mortality of 26 per cent as against a usual death rate of 50 per cent The activity of the serum was 1 50 000 that is to say a guinea pig which received 1/50 000 of its weight of serum survived a dose of toxin which invariably killed in 30 hours Actually Roux Martin and Chaillou injected 20 cc of serum under the skin of the flank Considering the severity of diphtheria in Paris at this time the results were promising among 120 cases of pharyngeal diphtheria only 9 patients died, whereas among 24 cases complicated by severe streptococcal infections 21 died So too among patients with "croup" requiring tracheotomy the mortality was 67 per cent Could one do better? We are convinced that it is possible But it will be the consequence not of

a mortality of over 25 per cent "Diphtheria appears recently to have again taken on a malignant character" They emphasized the importance of early intensive therapy preferably in hospital, if the patient was to be saved Reports of similar severe epidemics soon came from all over Europe they are listed by J S Anderson F C Happold J W McLeod and J G Thomson ("On the existence of two forms of diphtheria bacillus—*B diphtheriae gravis* and *B diphtheriae mitis*—and a new medium for their differentiation and for the bacteriological diagnosis of diphtheria" J Path & Bact 34 667 1931) These writers felt that the two types were associated with severe and mild cases and that they could be distinguished by growth on a special medium A thorough review of the subject with a bibliography of nearly three hundred titles is that of J W McLeod ("The types mitis intermedius and gravis of the Corynebacterium diphtheriae" Bact. Rev 7 1 1943) McLeod accepts three well defined cultural types of diphtheria bacillus The mitis strains cause mild diphtheria with occasional deaths from obstructive phenomena the intermedius and gravis forms may produce the malignant type The relation of various types to toxin production and response to antitoxin are discussed A M Fisher and S Cobb ("The clinical manifestations of the severe form of diphtheria" Bull. Johns Hopkins Hosp 83 297 1948) have recently discussed the severe form of diphtheria as seen in this country

The complexity of the whole problem of factors affecting the incidence of diphtheria is brought out by W T Russell (*The Epidemiology of Diphtheria during the Last Forty Years* [Medical Research Council Special Report Series" No 247 (London His Majesty s Stationery Office 1943)])

22 RAMON G Anatoxine diphtérique ses propriétés—ses applications Ann Inst Pasteur 42 959 1928

G Ramon (Sur le pouvoir floculant et sur les propriétés immunisantes d une toxin diphtérique rendu anatoxique [anatoxine]" Compt rend Acad d sc 177 1338 1923) had worked on this subject for years and had shown that "a diphtheria toxin which has completely lost its toxic effect on animals can still be precipitated by antitoxins" He raised the question to what extent such "ana toxine" still provoked the body to produce antitoxin. "Thanks to its innocuousness and the high degree of immunity which it confers it seems equally indi cated for antidiphtheric vaccination of the child" This work led to Ramon s monumental paper in which he discussed the preparation of anatoxin by the combined action of addition of formaldehyde to the toxic filtrate and subse quent heating for several weeks at low temperatures (38 –40 C) until toxicity had disappeared Guinea pigs injected with this material showed no signs of poisoning and when challenged with potent toxin after 3 or 4 weeks were found to be immune The sera of horses receiving several injections of this ana toxin became highly antitoxic Ramon quotes references to the literature on early experiences in human immunization by anatoxin He insisted on a definite technique as follows "Make a first subcutaneous injection of 0 5 cc. then after an interval of 3 weeks a second injection of 1 cc and 15 days later an injection of 1½ cc Such is diphtheria anatoxin A simple antigen easy to prepare and handle diphtheria anatoxin gives us a safe and inoffensive means of immunizing animals it gives us a practical and safe method of conferring on man a specific antitoxic immunity solid and durable and thereby permits us

In the later paper he gave statistics on the frequency of positive tests and pointed out that almost all the newborn gave negative skin reactions because they still had antitoxin derived from the mother He now developed the test more as an indication of whether prophylactic injections of antitoxin were necessary in groups of children who had been exposed to the disease In spite of certain difficulties the Schick test has been found very useful in epidemiological work Modern summaries of the problem are those of S Dudley ("Schick s test and its applications Quart J Med 22 321 1929 *The Schick Test Diphtheria and Scarlet Fever A Study in Epidemiology* ["Medical Research Council Special Report Series No 75 (London His Majesty s Stationery Office 1923)])

20 BEHRING E von Ueber ein neues Diphtherieschutzmittel Deutsche *med Wchnschr* **39** *873 1139 1913*

In spite of the brilliant discovery of diphtheria antitoxin cure of clinical cases was not always easy or satisfactory Toxin rapidly became anchored to body cells and was then no longer susceptible to neutralization by antitoxin it was necessary therefore to treat the patient early if good results were to be obtained in severe cases

The attention of investigators turned more and more therefore to methods of prophylaxis Von Behring following the suggestion of Theobald Smith ("The degree and duration of passive immunity to diphtheria toxin transmitted by immunized female guinea pigs to their immediate offspring J M Res **16** 359 1907 Active immunity produced by so-called balanced or neutral mixtures of diphtheria toxin and antitoxin" J Exper Med **11** 241 1909) who laid the experimental groundwork in guinea pigs introduced the method of immunizing people by injections of toxin and antitoxin mixtures which therefore is the direct precursor of modern immunization with toxoid "My new medicine is a mixture of very strong toxin and antitoxin in such proportion as to elicit in guinea pigs none or at most a very slight toxin effect Injection of this material led to the production of antitoxin in human recipients Von Behring discusses in detail the quantitative relationships indications contra indications and other relevant matters

But despite the fact that toxin antitoxin injections usually had a high immunizing value they were not always safe sometimes toxin and antitoxin became dissociated or there might be serum reactions (see B White and E Robinson Effect of exposure to low temperatures on diphtheria toxin antitoxin mixture" J A M A **82** 1675 1924) This led to further attempts to make immunization a harmless procedure (see Ref 22)

21 DEICHER H and AGULNIK F Ueber gehauftes Auftreten ungewohnlich bosartiger Diphtherie Deutsche med Wchnschr **53**:825 1927

Diphtheria incidence had fallen greatly following the introduction of methods of active immunization and mortality in 1925 had dropped to approximately 5 per cent Deicher and Agulnik in 1926 became aware of a radical alteration in the character of diphtheria There appeared patients mostly with the pharyngeal or nasal type desperately ill who apparently died of cardiac failure or vasomotor collapse highly refractory to ordinary antitoxin therapy and with

Section 15

TETANUS

Clinical	Refs 1 2, 3 4
Cultivation of tetanus bacillus	Ref 8
General	Refs 1 2, 3 4
Prophylaxis	Refs 15 16 19
Tetanus in animals	Refs 6 7
Tetanus antitoxin	Refs 9 10 11 15 18
Tetanus bacillus	Refs 5 7
Tetanus toxin	Refs 8 9
Therapy general	Refs 2, 3 4 21
Therapy intrathecal	Ref 14
Therapy penicillin	Ref 20
Toxin fate in body	Refs 12, 13 17
Toxoid	Ref 16

to do battle with diphtheria an epidemic disease There follows a long article by L Martin, G Loiseau and A Laffaille ("L Immunization antidiphtérique par l anatoxine chez l'homme Applications à la prophylaxie de la diphtérie Ann Inst Pasteur **42** 1010 1928) which goes into immunization in great statistical detail as checked by Schick tests Still other articles on the subject follow in the same number of the Annals

A T Glenny C G Pope H Waddington and V Wallace (XXIII The antigenic value of toxoid precipitated by potassium alum J Path & Bact **29** 38 1926) first showed that precipitation of toxoid by alum increased its antigenicity Glenny and Barr ("The precipitation of diphtheria toxoid by potash alum J Path & Bact **34** 131 1931) continued this work and later Barr Pope Glenny and Linggood ("Preparation of alum precipitated toxoid for use as an immunizing agent" Lancet **2** 301 1941) described in detail the practical preparation of the material

The whole subject of prevention of diphtheria is reviewed by Andrewes *et al* (*op cit* pp 349 ff) and recent discussions are those of J Jepson (Immunization of adults against diphtheria and tetanus New England J Med **251** 459 1954) and of G Edsall ("Active immunization New England J Med **241** 18 1949)

23 MUELLER J Howard Nutrition of the diphtheria bacillus Bact Rev 4 97, 1940

An authoritative review of the modern problems of bacterial nutrition with reference to diphtheria

24 WEINSTEIN Louis The treatment of acute diphtheria and the chronic carrier state with penicillin Am J M Sc **213** 308 1947

As long ago as 1929 Alexander Fleming ("On antibacterial action of cultures of a *Penicillium* with special reference to their use in the isolation of *B influenzae* Brit J Exper Path **10** 226 1929) showed that penicillin had a definitely inhibitory effect on *C diphtheriae* in the test tube Weinstein reviews attempts to treat clinical diphtheria with this antibiotic and points out that no definite curative effects have been obtained His own observations led him to a similar conclusion "Penicillin has no effect on the clinical course of diphtheria and its use in this disease does not eliminate the necessity of administering adequate amounts of antitoxin However penicillin in adequate dosage definitely shortened the duration of the carrier state (see Ref 18)

that they are the same disease Howship speculated on the nature of tetanus "It seems to creep as it were from the wound upwards to the origin of the nerve from thence extending its influence to the whole nervous fabric of the sensorium emanating as from a centre in the various course of the particular nerves distributed throughout the body and extremities Here one sees a vague groping toward the theory of neural transmission although Howship had of course no idea of any specific or concrete agent The question of whether amputation would prevent the progress of tetanus was a live one at the time Howship reports cases in which amputation was followed by recovery and also those in which it failed In another case pressure was tried "to effectually prevent the passing up of the irritating impression from the wound" but the patient was not saved He reports "a rare case of complete Tetanus from which the Patient recovered" without benefit of special therapy (the wound was in the foot, and the incubation period was 10 days) and also a case in which "Opium certainly checked the Progress of the Disease and probably saved the life of the patient" Finally there is a keen essay on the differentiation of the spasms of tetanus from epileptic seizures

2 LARREY D J Mémoires de chirurgie militaire et campagnes Vol 1: Mémoire sur le tétanos traumatique p 235 Paris J Smith 1812

Although tetanus had been described for centuries and the terms "tetanus" "locked jaw" "opisthotonus" and "trismus" etc were in common use at the turn of the eighteenth century most of the current articles were slight and dealt with some special therapeutic agent or method or with a report of a single case Baron Larrey s description is outstanding Most of his cases followed military gunshot wounds He first defines the terms "tetanus" "emprosthotonus" and "opisthotonus" "One can differentiate tetanus on the basis of greater or lesser intensity into acute and chronic The first is very dangerous and usually fatal [p 238] In complete tetanus the limbs are stiff the entire body becomes stiff so that in grasping one of the extremities one can lift the body like an inflexible mass" (p 239) Everything progresses rapidly so that very often within 24 hours the patient can no longer swallow or only with the greatest difficulty "Sometimes he is delirious the pulse is small and rapid, a rise of fever ordinarily takes place toward evening He loses weight under ones eye and feels terrible pain Stiffness increases he finishes his unhappy course by the third fourth fifth or seventh day (p 240) Larrey describes cases following various military actions but has nothing useful to suggest as to cause and no particular treatment He thought that he had saved several patients by amputation early after symptoms appeared

No less interesting is the account by Sir James Macgregor ("Sketch of the medical history of the British armies in the peninsula of Spain and Portugal during the late campaigns" M Chir Tr 6 381 1815) of tetanus in the Peninsular Wars "This very formidable disease was always very prevalent among the wounded after the great battles among several hundred cases there are few where this disease had made any progress in which remedies however varied seemed to have any influence on it He reports cases in which the effect of various therapeutic agents was obviously *post hoc* such as one in which the patient recovered apparently in consequence of long continued

Section 15

TETANUS

CURLING's book on tetanus (Ref 4) contains a summary of everything of importance known about the disease to date (1836) It also has a thorough bibliography beginning with the year 1668 The monumental volume by Edmund Rose (*Der Starrkrampf beim Menschen* [Stuttgart Ferdinand Enke 1897]) deals in its six hundred page with every phase of the subject The best general modern account of tetanus with bibliography is to be found in G S Wilson and A A Miles (Topley and Wilson's *Principles of Bacteriology and Immunity* [4th ed, Baltimore Williams & Wilkins Co 1955] 2 1955)

1 HOWSHIP, John[1] On lock jaw with tetanus M & Phys J London 21 180 1808

This is the first of a series of notes on tetanus by Howship which appeared in this journal over a period of three years as follows "Observations on lock jaw and tetanus with cases *ibid* p 407 "Observations upon the phenomena and treatment of tetanus with cases *ibid* p 446 Cases of lock jaw and tetanus" *ibid* 22 120 1809 Case of tetanus *ibid* p 185 "Lock jaw and tetanus" *ibid* p 324 Cases of tetanus" *ibid* p 396 Cases of tetanus *ibid* p 479 Observations upon tetanus *ibid* 23 15 1810 These reports give a good idea of the status of the subject a hundred and fifty years ago "The very limited knowledge we at present possess in the successful treatment of Lock Jaw and Tetanus must impress the mind of every anxious student in pathology with the conviction that very much remains to be acquired in this department of medical information To those who have read of but have never seen these complaints the histories already written and the plans of treatment proposed and described by writers of intelligence may be satisfactory but to such as have been in the habit of watching the various changes in this disease at the bedside of the unfortunate sufferer it does and must appear that we are not yet acquainted with any one medicine or application upon which from uniform experience we can rely nor are we possessed of any remedy that can be exhibited in any confidence of its power to afford relief" A number of vivid case reports are presented with critical evaluation of various methods of therapy such as mercurial inunctions—a popular method of treatment at the time but useless in Howship's hands Indeed William Charles Wells (A case of tetanus with observations on that disease Tr Soc Improvement M & Chir Knowledge 3 241 1812) reported a case occurring "during a salivation from the use of mercury" So intrenched was the use of mercury in tetanus however that Wells goes on to say It will perhaps appear to many as an obvious conclusion from the preceding case that mercury ought no longer to be regarded as a remedy for tetanus But so unstable are the grounds upon which we frequently build our reasonings in medicine etc" Sir James Macgregor (Ref 2) referred to a similar case He discussed the relation of lockjaw to tetanus and concluded

[1] This was the Howship of Howship's lacunae His interesting paper on "Microscopic observations on the structure of bone" is to be found in M Chir Tr., 7:387 1816

and spasmodically drawn and he could only by a great effort open his mouth about a quarter of an inch and imperfectly protrude his tongue At intervals of a few minutes severe spasms drew him backwards and these recurred upon the least excitement or when he made any effort to answer questions He was covered with perspiration pulse 100 respiration 20 tongue moist His occupation was that of a fellmonger or parchment worker He denied most positively having met with any accident puncture or cut whatever but he had one or two slight excoriations along the edges of the middle and ring fingers of his right hand caused by the friction of a brush which he was in the habit of using when rubbing quick lime over the skins These excoriations seemed nearly healed over giving him neither pain nor uneasiness and had it not been that the rag with which one was covered attracted my eye he would have made no mention of the circumstance nor did I at the time attach much importance to it The day of his admission was the fifth day of his symptoms for he stated that on the 13th he first perceived a stiffness in his jaw which had gradually increased to the present time but he was able to continue his work until the 16th the day before his admission when in walking along the street he was seized with a sudden spasm so severe as to throw him to the ground and from that time the symptoms increased rapidly"

Bright then along with his daily notes gives the therapeutic prescriptions for example on August 17

"Applicentur Cucurbitulae cruentae inter scapulas et detrahatur sanguis ad uncias octo—Hydrarg Submuriat gr iii Opii purif gr i Antimon tartar gr ¼ fiat pilula quarta quaque hora sumend a—Habeat Decoct Cinchonae ℥ iss quinae sulphat gr ii Tinct Cinchon comp ʒ i secunda quaque hora"

By September 14 "Bowels regular appetite good and nothing of the complaint remains except some rigidity of the muscles of the face"

Bright refers to a previous patient who also recovered "To these observations I have but little to add The treatment of the case now before us was conducted precisely on the principles here laid down and the same combination of tonic and stimulant remedies with calomel and opium was adopted as that by which the former case was brought to a successful issue It is scarcely to be supposed that perseverance in the use of tonic remedies with only two days intermission for a space of twenty days—during which the patient took nearly two ounces of sulphate of quinine and drank daily from fourteen to eighteen ounces of wine besides taking ammonia and brandy—could have failed to produce some powerful effect upon the constitution"

4 CURLING Thomas Blizard A treatise on tetanus London J G & F Rivington 1836

Curling's book is an admirable summary of knowledge of tetanus to date "The following essay on Tetanus one of a class of diseases but little understood and exceedingly difficult of investigation was not originally intended for publication Having no novelties in treatment to recommend I am induced to submit this imperfect performance to the notice of the profession in con equence of the desultory nature of the literature of this disease I have also endeavored to obtain from amongst the discrepant statements and conflicting opinions of different writers those conclusions which their collective experience would appear to justify and from amidst a host of remedies that have been employed to

accidental exposure to severe wet and cold The symptoms are stated to have been unusually severe As it was impossible to think of leaving the man he was carried on a bullock cart after the battalion During the first part of the day he was drenched with rain but after ascending one of the highest mountains in Gallicia the snow was knee deep and the thermometer below 30 The patient was exposed to this inclement weather from six o clock in the morning till ten at night when he arrived half starved to death but perfectly free from every symptom of tetanus"

Other good results are attributed to laudanum and warm baths although Surgeon Brown saw several cases at Elvas where opium was the favorite remedy and every case so treated died" Venesection and purgation of course had their advocates "This terrible disease is too easily distinguished to require detailed description It occurs in every description and in every stage of wounds from the slightest to the most formidable from the healthy and the sloughing from the incised and lacerated from the most simple and most complicated It occurs at uncertain periods but it is remarked that if it does not occur for 22 days from the date of the wound the patient is safe Mr Guthrie divided the disease according to its short duration or protraction into two species viz acute and the mild which he thought were independent of peculiarity of constitution The remedies which have been chiefly trusted to for the cure of this formidable disease are opium mercury wine warm and cold bath venesection ipecacuanha and digitalis in large doses enlargement of the original wound and amputation of the limb These have been tried alone and in various combinations and I am obliged to confess that the whole failed in almost every acute case of tetanus which occurred Amputation as recommended by the baron Larry [sic] totally failed in the fully formed disease it was tried in many cases at Toulouse Indeed I believe this gentleman s opinion is altered since he published the result of his experiences in Egypt I have been recently informed by Mr Guthrie that the baron distinctly acknowledged to him that the loss of the French army after the battle near Dresden was principally from tetanus when of course this practice must have been fairly tried

All this gives a vivid impression of the doctor s helplessness in the face of a disease the cause of which was unknown even though the clinical associations were obvious

3 BRIGHT [Richard] Case of tetanus in which quinine and stimulants were administered very extensively with success Guy s Hosp Rep., I 111 1836

As we have already indicated the medical journals at this period were full of reports of single cases of tetanus presumably cured by some special drug or procedure The great Richard Bright fell into the same error His case is reported with vividness and accuracy but one doubts whether the therapy had anything to do with recovery "W Turner aged 38 was admitted under my care into Guy s Hospital the subject of confirmed tetanus of four days standing When I first saw him he was lying on his bed perfectly stiff with his legs stretched out and his feet bent almost backwards his abdomen was hard and unyielding as a board all the muscles of his thighs and legs were tense he was scarcely able to bend his fingers his cheeks and forehead were wrinkled

elicit a symptom complex practically always lethal featured by persistent cramplike contractions of certain muscle groups and by periodic violent extensor spasms of practically all the muscles of the body and extremities which must be designated as tetanus" In mice in which a little earth was introduced into a "pocket" near the tail after a latent period of 1½–2½ days spasm of the muscles of the hind legs appeared In the 12–20 hours before death took place the animals showed periodic violent extensor spasms of neck and back These spasms occurred not only spontaneously but on touching the animal tapping the table etc A similar picture was produced in rabbits and guinea pigs but not in two dogs If the inoculation was made in the neck the upper extremities went into spasm first Autopsies showed no generalized lesions but in pus from the site of inoculation there were always seen narrow long bacilli which stained best with fuchsin" In several cases these bacilli were present in immense numbers Nicolaier suggested that one was dealing with an infectious tetanus caused by micro-organisms He thought that the presence of a fairly long incubation period was in favor of this view He heated earth which had produced tetanus for an hour at 190 C and found that mice injected with it remained healthy on the other hand filtrates of a suspension of unheated earth produced the disease He tried to cultivate the organism with dubious success and he was not able to isolate it in pure culture although he stated that he had produced tetanus with the seventh generation grown on blood serum At any rate he concluded that "through these experiments it is shown that bacilli exist which produce tetanus by penetrating deeply into wounds He concluded that the disease was not caused by massive growth of the bacilli through the body but that they produced locally a poison which resembled strychnine in its action Finally the bacilli were found in street dirt gardens orchards etc they were not found in soil from "the woods" He raised the question of whether human tetanus is not due to contamination of wounds by soil

As one can see Nicolaier s studies were of fundamental importance indeed he discovered or sensed correctly most of the chief facts about the cause and production of tetanus P Fildes ("Tetanus I Isolation morphology and cultural reactions of B tetani" Brit J Exper Path 6 62 1925) devised a ready method for isolation of tetanus bacilli in pure culture He found them 33 times among 70 soil specimens (cultivated and waste lands) 34 times in 200 specimens of horse feces (London stable horses) and twice in 200 specimens of human feces (hospital patients) These findings have been generally confirmed throughout the world in numerous papers

6 CARLE and RATTONE Studio esperimentale sull eziologia del tetano Communicazione preventiva Gior Accad med Torino 32 174 1884

Although numerous attempts had been made to produce tetanus in animals by injection of material from tetanus cases Carle and Rattone seem to have been the first who were definitely successful They stated that they would attempt to determine whether tetanus was a "neurosis" or an infectious disease They injected into the sciatic nerve sheath of 21 rabbits a suspension of material from an acne pustule from which fatal tetanus had developed All these animals died of the disease Carle and Rattone were also able to pass tetanus from animal to animal by injection of a suspension of nerve from above the site of inoculation

trace to some general cause or mode of operation the salutory influence which they have been supposed to exert"

The book is based on an analysis of 128 cases of traumatic tetanus which are summarized in tabular form in an appendix and there follows a bibliography of some 150 references mostly to more or less contemporary case reports The opening chapter gives first a definition of terms such as emprosthotonous" opisthotonus "plerosthotonus etc and then takes up the clinical features prognosis and diagnosis in detail

Chapter ii on the pathology of tetanus, is to some extent a dead letter as modern students agree that there are no visible lesions in uncomplicated cases However there are some points of historical interest "Although the phenomena distinguishing Tetanus are chiefly expressed in deranged action of the muscles yet it is very generally admitted that some part of the nervous system is the source or actual seat of the disease The following appearances are often presented by the brain and its membranes congestion of the sinuses the vessels of the pia mater filled with florid blood more or less increased vascularity of the cerebral substance slight serous effusion between the membranes and the ventricles" (p 45) Inflammation and disorganization of the sympathetic ganglia were also described and "the nerves have in several instances been found injured and inflamed at the seat of the original wound" (p 66) Still other lesions are described elsewhere in the body As to the nature of the disease "Tetanus then *appears to consist in a peculiar morbid action in the tractus motorius* the intimate nature of which is altogether beyond our comprehension" Irritation as this action is called is sharply and correctly differentiated from inflammation It appears then that the older observers came as near to understanding the nature of the disease as was possible without knowledge of the specific soluble toxin Curling finally concludes "Tetanus is a functional disease of the nervous system that is to say a disease unaccompanied with any perceptible lesion of structure the nature of which although essentially distinct from inflammation is completely unknown There are therefore no morbid changes peculiar to Tetanus and by which it can be recognized" (p 121)

Under Treatment the question of amputation (see Refs 1 2) is discussed at length and also the division of nerves As to constitutional treatment a long list of agents is critically discussed—purgatives mercury bloodletting counter irritation opium tobacco antimony cold affusion the warm bath the vapor bath tonics and stimulants carbonate of iron hydrocyanic acid and other remedies *Curling concludes Perhaps for acute Tetanus a sure* and safe remedy in all cases is yet to be discovered But if we clearly understand the indications to be fulfilled and direct our treatment accordingly we are infinitely more likely as science advances to find out this remedy than by groping in the dark or by disregarding the lights of experience and stumbling where others have failed before us" (p 206)

Not much further advance was made in the subject until the discovery of the bacillus fifty years later

5 NICOLAIER Arthur Ueber Infectiosen Tetanus Deutsche med Wchnschr 10 842 1884

"In the course of extensive examination of soil bacteria it appeared that implantation of certain samples of earth into mice rabbits and guinea pigs could

subcultures the bacilli were still "virulent" as were spores kept in the desiccator for several months

The importance of this work done in the laboratory of R Koch can hardly be overestimated

9 BEHRING [E] and KITASATO [S] Ueber das Zustandekommen der Diphtherie Immunitat und der Tetanus Immunitat bei Thieren Deutsche med Wchnschr **16** 1113 1890

This is the classical article of Behring and Kitasato dealing with antitoxic immunity both in diphtheria and in tetanus "The immunity of rabbits and mice which have been immunized against tetanus rests on the capability of cell free blood serum to render harmless the toxic substances which the tetanus bacilli produce" This short sentence summarizes the principles of antitoxic immunity More in detail the authors state "(1) Blood from rabbits immune to tetanus possessed the property of destroying tetanus toxin (2) This property is demonstrable also in extra vascular blood or in its cell free serum (3) These properties are so persistent that they remain effective in the body of other animals so that one can achieve outstanding therapeutic effects by blood or serum transfusions (4) The tetanus toxin–neutralizing properties are absent in the blood of such animals as are not immune against tetanus and if one introduces tetanus toxin into non immune animals it can be demonstrated after the death of the animals in the blood and other body fluids" Simple experiments supporting these theses are next described The toxin is intensely potent "0 00005 cc of filtered bacteria free 10-day culture of tetanus bacilli is enough to kill a mouse in 4–6 days" But 0 2 cc of a mixture of 5 cc of serum from a rabbit immune to tetanus and 1 cc of culture—in other words more than two hundred times the fatal dose of toxin—is harmless

Kitasato (Experimentelle Untersuchungen uber das Tetanusgift" Ztschr f Hyg u Infektionskr **10** 267 1891) soon gave a more detailed account of the tetanus toxin He explained details of filtration methods whereby the material was made absolutely bacteria free and reported animal experiments with the filtrate in which all the findings of tetanus were reproduced "One can now state definitely that one is dealing not with an infection but with an intoxication Tetanus bacilli produce a substance with specific toxic action" Small animals treated with filtrate developed tetanus in at least 3 days If they remained well until the fourth day they did not develop tetanus Transfer of tissues from dead animals was ineffective but blood or pleural fluid from such animals always produced tetanus "This proves that tetanus toxin penetrates into the blood stream" The effects of heat drying etc on the potency of filtrates were next discussed and then the influence of many chemicals Finally Kitasato described attempts to immunize animals It was not possible to produce immunity by accustoming the animals to increasing doses of toxin nor could immunity be produced by injecting filtrates heated at increasing temperatures Chickens were found refractory to tetanus but chicken blood was ineffective as an immunizing agent

10 BEHRING and FRANK Experimentelle Beitrage zur Lehre von der Bekampfung der Infectionskrankheiten Ueber einige Eigenschaften des Tetanusheilserums Deutsche med Wchnschr **18** 348 1892

They concluded that (1) human tetanus is an infectious disease (2) it can be transmitted from man to rabbit (3) it can be transmitted from rabbit to rabbit

7 ROSENBACH Zur Aetiologie des Wundstarrkrampfes beim Menschen Arch f klin Chir 34 306 1887

Rosenbach seems to have been the first to demonstrate bacilli of tetanus in man He used bits of decomposing tissue from a patient with gangrene of the feet who had succumbed to the disease Guinea pigs inoculated with this material promptly died of typical tetanus of which he gives a beautiful description In the pus from the human subject were found all sorts of bacteria including bacilli resembling those described by Nicolaier (Ref 5) Rosenbach used anaerobic methods and like Nicolaier was unable to isolate the bacilli in pure culture but he produced tetanus with certain cultures He saw and described the familiar drumstick appearance which he recognized as due to spores Rosenbach raised the following important questions "Does the tetanus bacillus spread through the body? "If so in what manner does this spread take place?" "What relation has it to the nervous system to the spinal cord?

8 KITASATO, S Ueber den Tetanusbacillus Ztschr f Hyg u Infektionskr 7 225 1889

The work of Nicolaier (Ref 5) and of Rosenbach (Ref 7) was soon confirmed by many writers but as late as 1889 Widenmann ("Beitrag zur Aetiologie des Wundstarrkrampfes" Ztschr f Hyg u Infektionskr 5 522 1889) cast doubt on the previous observations He found that material from a tetanus wound in a man implanted in mice did to be sure produce tetanus promptly "but in not a single case were the slender spore bearing bacilli designated by most authors as 'Tetanusbacilli found. To this communication was attached an addendum by the great Carl Flugge in support of Widenmann

Kitasato felt that to settle this question it was necessary to isolate the spore-bearing bacilli in pure culture He found that surface growth of material from tetanus always showed a mixture of many other organisms with the "Tetanus bacilli" it was the consumption of oxygen by the aerobes which perhaps allowed growth of the anaerobic tetanus bacilli. Kitasato therefore heated mixed cultures at 80 C for an hour to kill the aerobes and then planted them in an atmosphere of hydrogen. He thus obtained pure cultures of spore bearing bacilli which he described in detail and with these cultures he readily produced tetanus in small animals without the addition of foreign bodies The animals sickened in 24 hours and died in 2 or 3 days At autopsy hyperemia was found at the injection site but no pus or bacilli no changes were noted in the internal organs nor were tetanus bacilli to be isolated from them To find out how quickly the tetanus bacilli formed a soluble toxin the site of inoculation was excised and cauterized after various intervals Up to an hour the animals remained well if the excision took place after an hour the animals all developed tetanus Bacilli were seen at the injection site for 8–10 hours thereafter they disappeared without leaving a trace (*spurlos verschwunden*) He attributed the various conclusions of different authors to variability in formation of tetanus spores if the disease ran a quick course there might be seen bacilli without spores whereas spores were formed if the animal survived for a longer interval But the bacilli were always present Finally Kitasato noted that even after many

of recent tetanus statistics" Lancet 2 966 1917) came to no definite conclusion in favor of antitoxin and more recently R. W Huntington Jr W R Thompson and H H Gordon ("The treatment of tetanus with antitoxin" Ann Surg 105 93 1937) in an analysis of 642 cases concluded that "relatively little has been accomplished in the specific treatment of tetanus" These observations of course do not apply to the prophylactic use of antitoxin

12. MARIE A Recherches sur la toxine tétanique Ann Inst Pasteur **11** 591 1897

Marie reviews the primitive and conflicting work on what happens to tetanus toxin in the body and then takes up the subject anew First he notes that if one determines the lethal subcutaneous dose for a rabbit seven to eight times the amount must be given intravenously to produce a fatal effect This made him assume that in the first case "a part of the toxin has followed the course of the nerve fibers and has reached the spinal cord directly" To prove this he devised the following experiment A fatal dose of toxin was injected directly into the sciatic nerve On the day after inoculation the operated leg was stiff and on the following day was paralyzed with extensor contraction by the fourth day the tetanus was generalized and the animal died. But if one resects the second cervical nerve in a similar animal, allows the wound to heal, and then injects a fatal dose of toxin into the paralyzed paw the animal does not fall ill He then reports experiments to find out what becomes of toxin injected into the blood stream and concludes that it remains for a variable length of time in the blood but that when this time has "run out," there is no evidence of toxin remaining in organs or in glandular secretions He feels that extracts of organs from animals with tetanaus prepared by others and alleged to be toxic, produce if anything immediate reactions which have nothing to do with tetanus

Marie with V Morax ("Sur l absorption de la toxin tétanique" Ann Inst Pasteur 16 818 1902) later continued his studies He points out the specific effect of tetanus toxin on the motor neurons and attempts to determine "the mechanism of propagation of the toxin from its point of penetration to the sensitive cell." He devised experiments which he thought proved that an injection of toxin was taken up rapidly by the local motor nerves and traveled to the ganglion cells thus causing local tetanus Part of the injected toxin diffused into the blood stream and was more slowly absorbed by motor nerves in general, ultimately producing generalized tetanus

There is an immense literature on tetanus toxin which cannot be reviewed here However M J Pickett P D Holford and R O Germain ("Purification of high titre tetanus toxin" J Bact 49 515 1945) report purification of crude toxin by 125-fold and L. Pillemer R Willter and D B Grossberg ("The isolation and crystallization of tetanal toxin" Science 103 615 1946) prepared crystalline material which contained 50-75 million minimum lethal doses (mouse) per mg of N

13 MEYER, Hans and RANSOM Fred. Untersuchungen uber den Tetanus Arch f exper Path u Pharmakol **49** 369 1903

The work described in this classical article confirms parallels and extends that of Marie and Morax (Ref 12) After a review of the literature on the question of how tetanus toxin acts the writers lay down a series of propositions with

In an interesting article Behring (Die Blutserumtherapie bei Diphtherie und Tetanus Ztschr f Hyg u Infektionskr 12 1 1892) sketches the general principles of serum therapy He points out that in acquired immunity the cell free serum of the immune individual always contains protective bodies This blood should have protective and curative value for another individual Behring then goes into the subject in detail ("Ueber Immunisierung und Heilung von Versuchsthieren beim Tetanus" *ibid* p 45) in connection with prophylaxis and cure of tetanus in small animals He used sera developed in such animals but also horse serum prepared by Schutz (Versuche zur Immunisierung von Pferden und Schafen gegen Tetanus *ibid* p 58) In the paper with Frank, however he defined precisely the fatal dose of toxin for mice and demonstrated clearly the protective and curative value of the serum They noted early that even if treatment was begun at the very onset of symptoms at least a thousand times as much antitoxin was needed to save the animal as to protect it and that if the disease was advanced no amount of serum was adequate They felt that the serum should not be used in man until the experimental facts were worked out but they stated We believe that we can save people with tetanus with this serum which works a cure in mice Kitasato ("Heilversuche an tetanuskranken Thieren," Ztschr f Hyg u Infektionskr 12 256 1892) who was really working along with Behring at about the same time published similar results He emphasized especially the vastly greater quantity of serum necessary for cure than for prophylaxis but as yet gave no clear explanation

11 BEHRING [Emil Adolph] Das Tetanusheilserum und seine Anwendung auf tetanuskranke Menschen Leipzig Georg Thieme 1892

This little book contains four articles by Behring and his associates which bring up to date all the problems of serotherapy of tetanus The first is essentially an amplification of previous articles (Ref 10) and it deals with estimation of the minimum lethal dose of toxin and minimal effective doses of curative sera in small animals Behring again points out that even with the earliest clinical symptoms a thousand times the prophylactic dose of serum is necessary for cure whereas after 12 hours a hundred thousand times the prophylactic dose is necessary and that later no amount of antitoxin suffices He states that since certain patients with tetanus recover spontaneously serum therapy cannot be evaluated in individual cases but only by considering the mortality in large groups The second article deals with the use of antitoxin in human cases of tetanus Behring discusses the preparation of serum in horses and the general indications for its use He critically reviews reports in the Italian literature on serotherapy and questions the validity of the claims which are made (G Cattani L'Ematoterapia nel tetano Riforma med 2 769 1892 G Tizzoni and G Cattani Alcune questioni relative all immunita pel tetano Riforma med 3 495 1892) In the third article Dr Rotter discusses the treatment of a patient with tetanus which he follows with a general discussion It is pointed out that prognosis in tetanus depends on the duration of the incubation period and the speed with which clinical manifestations develop The shorter the incubation period the worse the prognosis Statistics are given These articles cover the whole subject and are definitive to date

In modern times a good deal of skepticism has grown up as to whether antitoxin has any beneficial influence in established tetanus F Golla ("An analysis

system by way of motor nerves Tetanal toxin spreads within the central nervous system Local tetanus is of central origin Our results provide conclusive evidence for the existence of the blood central nervous system barrier"

14 PARK William H and NICOLL Matthias Jr Experiments on the curative value of the intraspinal administration of tetanus antitoxin J.A.M.A 63:235 1914

Realizing that clinical results with subcutaneous injection of antitoxin in established cases of tetanus were not good Park and Nicoll experimented with intra spinal injection of antitoxin in guinea pigs which had received otherwise fatal doses of tetanus toxin "This would seem absolutely conclusive of the superiority of the intraspinal method of giving antitoxin over the intravenous method only those animals receiving antitoxin in the spine were able to survive" The writers also reported four human cases treated intraspinally who recovered During World War I C S Sherrington ("Observations with antitetanus serum in monkeys" Lancet, 2 964 1917) at the instigation of Bruce (Ref 15) studied the question of the most efficacious route of injection of antitoxin into monkeys He found a much greater number of recoveries in animals treated by the lum bar or bulbar subdural routes than by the subcutaneous or intramuscular routes The "Tetanaus Committee" of the British army concluded that the best method of treatment "lies in the earliest possible administration of large doses of antitetanic serum by the intrathecal route" (Bruce Ref 15) W M Firor ("Intrathecal administration of tetanus antitoxin" Arch. Surg 41:299 1940) working with dogs concluded that "the intracisternal injection of antitoxin into dogs suffering from early mild, or moderately severe tetanus yields far better results than intravenous injection In animals with severe tetanus there is little difference in the results but the difference favors the intracisternal route" Firor lists the variables which make clinical evaluation of treatment so difficult "(*a*) length of incubation period, (*b*) interval before treatment was begun (*c*) severity of symptoms (*d*) details of treatment (*e*) location of wound (*f*) age of the patient (*g*) the presence of other conditions which might have caused death, and (*h*) the culture of *Clostridium tetani* from the wound" J B Yodh ("Observations on the treatment of tetanus" Brit. M J 2 589 1932) wrote a paper which had much influence in which he reported better results in tetanus in man if the therapy included intrathecal (intracisternal) injection of antitoxin Nevertheless intrathecal therapy is not advised in current textbooks mainly because of the belief that only toxin which is freshly formed at the site of the wound is amenable to neutralization by antitoxin (Ref 21) and such workers as H M Smathers and M R Weed ("The treatment of tetanus" Arch. Surg 57 291 1948) actually found the same death rate for patients treated with and without antitoxin given intrathecally

15 BRUCE David Tetanus analysis of 1 458 cases which occurred in home military hospitals during the years 1914–1918 J Hyg 19 1 1920

As pointed out by the early workers (Behring Refs 10 11) even when in cipient symptoms are present much greater doses of antitoxin are necessary for cure than for prevention Hence the obvious moment to give the antitoxin is shortly after the suspicious wound is incurred Prophylactic use of antitoxin (passive immunization) was therefore heavily stressed especially before the

experiments to support them "(1) After subcutaneous inoculation the poison can be demonstrated in the nerves (2) Threatened centers in the spinal cord can be protected against the effect of tetanus toxin by blocking the afferent nerves with antitoxin (3) Ascending spread of the poison in the spinal cord is inhibited by transection of the cord (4) Consequences of injection of poison into nerves (tetanus occurs much more quickly than after subcutaneous injection) They show that tetanus occurs within a few hours after intramedullary injection into the spinal cord and they correlate the incubation period with the length of peripheral nerves in various animals Thus the incubation period is 4 or 5 days in man or horse as against 8–12 hours in mice

Meyer and Ransom formulated their theory of experimental tetanus poisoning as follows "At the point of inoculation toxin is absorbed from the lymph spaces by the endings of the motor neurones and by way of them reaches the motor spinal ganglion cells These are thrown into a state of hyperexcitability so that they are constantly stimulated by reflex sensory influences which are ordinarily subliminal Thus the spasms arise This theory was accepted without much opposition until recent years, when it was questioned as for example by Abel (Ref 17) There is much further material in this classical article which really must be studied in the original

U Friedemann and his associates tried to settle the controversy which had sprung up on the question of the transport of tetanus toxin by nerves Friedemann and B Zuger who had been working on the general subject of "Quantitative studies on the neutralization of pathogenic agents in tissues by circulating antibodies (J Immunol 36 192 205 219 1939) were led to study tetanus toxin antitoxin relationships (U Friedemann B Zuger and A Hollander "Investigations on the pathogenesis of tetanus I The permeability of the C N S barrier to tetanal toxin Passive immunity against toxin introduced by various routes" J Immunol 36 473 II The influence of section of the nerves on the neutralization of intramuscularly injected tetanal toxin by circulating antitoxin *ibid* p 485 U Friedemann A Hollander and I M Tarlow "III J Immunol 40 325 1941) This work on the whole confirmed that of Meyer and Ransom and rendered untenable the views of Abel and his associates The principal experiments were these From 5 to 80 times more circulating antitoxin is required to protect guinea pigs from death after the intracutaneous and intramuscular than after the intravenous injection of tetanal toxin The intramuscularly injected guinea pigs may die despite the presence of free antitoxin in the blood" They concluded therefore that there was a blood barrier to the central nervous system which was impermeable to toxin and that intramuscularly injected toxin must reach the central nervous system by some other route namely the nerves This position was supported by the work reported in the second communication which showed that section of the femoral and sciatic nerves abolishes the differences in the amounts of antitoxin required to neutralize intramuscularly and intravenously injected tetanal toxin The third paper is a critical analysis of the literature on the whole subject It is pointed out that it is now known that a good many viruses and chemical substances are transmitted to the central nervous system by transport along nerves and the following final conclusions are drawn "Tetanal toxin does not reach the central nervous system directly by way of the circulation Tetanal toxin reaches the central nervous

practice to combine several antigens for prophylactic immunization in one injection (see e g J J Miller J B Humber and J O Downie "Immunization with combined diphtheria and tetanus toxoids [aluminum hydroxide adsorbed] containing Hemophilus pertussis vaccine" J Pediat 24 281 1944) The use of active immunization became standard in the United States Army during World War II and is described by A P Long ("Tetanus toxoid its use in the United States Army" Am J Pub Health 33:53 1943) This program was followed by the disappearance of tetanus from the army barring a very occasional case in an unimmunized person

An international unit for toxoid has been defined (Expert Committee on Biological Standardization *Fifth Report* [Geneva World Health Organization July 1952] p 5 ["Technical Report Series No 56])

17 ABEL, J J EVANS E A Jr HAMPIL, B and LEE F C Researches on tetanus II The toxin of the Bacillus tetani is not transported to the central nervous system by any component of the peripheral nerve trunks Bull Johns Hopkins Hosp 56 84 1935

Although the theories of Meyer and Ransom (Ref 13) are generally accepted there have been dissenting opinions Among these of special note are the views of J J Abel the eminent Johns Hopkins pharmacologist Abel was attracted to the problem from a general study of poisons ("On poisons and disease and some experiments with the toxin of the Bacillus tetani" Science 79 121 1934) A long series of papers followed which we cannot attempt to review in detail Suffice it to say that Abel makes a strong case on the grounds of both reasoning and experiment against the neural transmission of tetanus toxin Thus the second paper of the series is largely a critique of the literature it is with reference to local tetanus not resulting from neural transmission to the central nervous system that he bases a large part of his case In another paper (J J Abel B Hampil, and A F Jonas Jr "III Further experiments to prove that tetanus toxin is not carried in peripheral nerves to the central nervous system" Bull Johns Hopkins Hosp 56 317 1935) Abel reports that injection of toxin into the dog s sciatic nerve fails to be followed by local tetanus when a much smaller dose injected subcutaneously or intramuscularly does produce it The fourth paper of the series (IV Some historical notes on tetanus and commentaries thereon" *ibid* 57 343 1936) consists of a most interesting critical review of the literature bearing on Abel s thesis The ninth paper (J J Abel W M Firor and W Chalian "IX Further evidence to show that tetanus toxin is not carried to central neurons by way of the axis cylinders of motor nerves Bull Johns Hopkins Hosp 63 373 1938) summarizes and fortifies with more experiments Abel s views He concludes "The history of science bears testimony to the fact that it is not easy to dislodge from the mind a theory that has long been wholeheartedly accepted We have therefore presented in this paper more arguments than might seem necessary to disprove the validity of the nerve carriage theory of tetanus toxin We have therefore reviewed critically the main arguments that have been adduced in the past in favor of the theory and have shown that each of them may be refuted and have given further evidence to show that tetanus toxin can be carried to the tissues of the body whether these be the specifically reacting striated muscles and motor horn cells or structures that do not respond in a recognizable manner to the action of

days of active immunization with toxoid (Ref 16) This important analys s by Bruce shows how the incidence and mortality of tetanus fell off after prophy lactic immunization was introduced into the British army in World War I

Bruce also discusses the curative use of antitoxin after the disea e is pre ent and points out the difficulties in evaluation because of many variables Among 1 458 cases who had had injections of antitoxin after symptoms developed 33 5 per cent died

The article contains much interesting material on other aspects of tetanus

16 DESCOMBY P L Anatoxine tétanique Compt rend Soc de biol 91 239 1924

G Ramon (Anatoxine diphtérique, ses propriétés—ses applications" Ann Inst Pasteur 42 959 1928) had shown that diphtheria toxin could be rendered harmless while retaining its antigenic value by the action of formaldehyde and heat (anatoxin) Descomby used the same method with tetanus toxin with milar results Guinea pigs withstood 5–10 cc of such anatoxin which before modification was fatal in doses of 1/10 000 cc Tetanus anatoxin also had a high antigenic value A horse for example after two injections of 15–20 cc of anatoxin at intervals of 14 days became resistant to 1 cc of a toxin which was about thirty times the fatal dose Ramon and Zoeller (L Anatoxine tetanique et l immunization active de l'homme vis à vis du tétanos" Ann Inst Pasteur 41 803 1927) soon discussed in detail the theoretical and practical uses of anatoxin in man They point out that passive immunization is transient and can be combined with active immunization with anatoxin in two doses at intervals of 20 days They emphasize the value of active immunization in those likely to be subjected to trauma such as military personnel and also advise the immuni zation of pregnant females to protect the child against "tetanus neonatorum" In another paper Ramon and Descomby ("L Anatoxine tetanique et la prophy laxie du tetanos chez le cheval et les animaux domestiques Ann Inst Pasteur 41 834 1927) discuss the immunization of domestic animals Later Ramon and Zoeller (Sur la valeur et la duree de l immunite conferee par l anatoxine tetanique dans la vaccination de l'homme contre le tétanos" Compt rend. Soc de biol 112 347 1933) summarize their results and demonstrate that the sera of people immunized several years earlier may still contain enough antitoxin to neutralize up to three hundred fatal guinea pig doses of toxin They now advise three doses of anatoxin (1 1 5 and 2 cc) at intervals to produce immunity They also sugge ted "booster doses (*injection de rappel*) at time of exposure (injury) to tetanus infection and found that they resulted in a great increase in the titer of antitoxin in the blood In this country (E M Lincoln and C K Greenwald Active immunization of human beings with tetanus toxoid" Proc Soc Exper Biol & Med 30 1241 1933) similar results were obtained D H Bergey (Active immunization against tetanus infection with tetanus toxoid" J Infect Dis 55:72 1934) soon found that as with diphtheria anatoxin pre cipitation with alum resulted also with tetanus anatoxin in active preparations F G Jones and J M Moss ("Studies on tetanus toxoid I The antitoxic titer of human subjects following immunization with tetanus toxoid and tetanus alum precipitated toxoid" J Immunol 30 115 1936) found that two injections of alum precipitated tetanus toxoid produced a higher immunity than did three injections of the unprecipitated toxoid It has become customary in pediatric

which it is impossible to eradicate the focus [or foci] surgically Bacteriologic studies revealed that Clostridium tetani could no longer be isolated from wounds in these patients twenty four hours after the first administration of penicillin" R S Diaz Rivera L Deliz and J Berio-Suárez ("Penicillin in tetanus" J.A M A 138 191 1948) reported a clinical analysis of fifty nine penicillin treated cases and concluded that the drug was useful although their statistics seem inconclusive But other observers such as L Lewis ("Therapeutic trial of penicillin in tetanus" Ann Int Med 25 903 1946) working in the armed forces could not convince himself that penicillin had any beneficial effect in tetanus

21 FORBES Gilbert B and AULD Marian Management of tetanus Am J Med 18:947 1955

A well-documented modern summary of the treatment of tetanus The authors make the point that recovery may depend on great attention to certain details of management rather than on antitoxin They stress the adequate use of muscle-relaxing agents attention to keeping an open airway and preventing secondary respiratory infection often including the use of tracheotomy skilled use of sedatives and the proper maintenance of fluids and electrolytes Still other details are touched on

toxin *only by the same mechanisms that effect the distribution of countless other drugs and poisons namely the blood and lymph vascular systems* The toxin exhibits both a central and a peripheral action each of which may be demonstrated independently of the other The central effect which is characterized by reflex motor convulsions is due to the poisoning of the motor nerve cells of the spinal cord, medulla and pons the peripheral effect recognized as the unremitting rigidity of voluntary muscles results from the fixation of the toxin upon the motor end organs" A M Harvey ("The peripheral action of tetanus toxin J Physiol 96 348 1939) comes to the support of Abel with work in which modern methods of studying the transmission of the nerve impulse were used He concludes "These experiments afford direct experimental evidence of a peripheral action of tetanus toxin in the region of the neuromuscular junction

We must leave the reader to study the original papers and to resolve this controversy for himself

18 ABEL J J EVANS E A Jr and HAMPIL B Researches on tetanus Distribution and fate of tetanus toxin in the body Bull Johns Hopkins Hosp **59** 307 1936

The question of how long after it is in contact with the tissues tetanus toxin is amenable to neutralization by antitoxin is paramount in planning treatment for patients Abel and his colleagues showed that up to a certain time toxin which is apparently fixed in the tissues can still be neutralized by an excess of antitoxin if administration of antitoxin is delayed too long the toxin is not affected by it These observations support the general feeling that therapy should be prompt and intensive

19 COOKE J V and JONES F G The duration of passive tetanus immunity J A M A **121** 1201 1943

The writers showed that while passive immunization with the usual dose of 1 500 units produced immunity for only about 3 weeks larger doses (100 000 units) conferred a much lengthier protection They found that the antitoxin interfered with active immunization with toxoid and advised deferring such immunization for several weeks

20 WEINSTEIN Louis and WESSELHOEFT Conrad Penicillin in the treatment of tetanus Report of two cases New England J Med **233** 681 1945

Following the observation (W E Herrell D R Nicholls and D H Heilman Penicillin its usefulness limitations diffusion and detection with analysis of 150 cases in which it was employed" J A M A **125** 1003 1944) that penicillin inhibited the tetanus bacillus in the test tube there appeared a brief note (R Buxton and R Kurman "Tetanus report of two cases treated with penicillin" J A M A **127** 26 1945) on two cases which recovered in which penicillin was employed in addition to antitoxin Weinstein and Wesselhoeft explored the matter more carefully They reported two more patients who recovered under penicillin and antitoxin therapy and they defined the rationale of using penicillin in tetanus "Penicillin appears to be of the greatest value in cases of tetanus infection in which no localized areas of bacterial invasion can be detected or in

which it is impossible to eradicate the focus [or foci] surgically Bacteriologic studies revealed that Clostridium tetani could no longer be isolated from wounds in these patients twenty four hours after the first administration of penicillin" R S Diaz Rivera L Deliz and J Berio-Suárez ("Penicillin in tetanus" J.A M A 138:191 1948) reported a clinical analysis of fifty nine penicillin treated cases and concluded that the drug was useful although their statistics seem inconclusive But other observers such as L Lewis ("Therapeutic trial of penicillin in tetanus" Ann Int Med 25 903 1946) working in the armed forces could not convince himself that penicillin had any beneficial effect in tetanus

21 FORBES Gilbert B and AULD Marian Management of tetanus Am J Med 18:947 1955

A well-documented modern summary of the treatment of tetanus The authors make the point that recovery may depend on great attention to certain details of management rather than on antitoxin They stress the adequate use of muscle relaxing agents attention to keeping an open airway and preventing secondary respiratory infection often including the use of tracheotomy skilled use of sedatives and the proper maintenance of fluids and electrolytes Still other details are touched on

Section 16

TYPHUS

Antityphus vaccination	Ref 14
Bacteriology	Ref 5
Brill's disease	Ref 8
Clinical	Refs 1 2 3 4 6
Control measures in typhus	Ref 18
Differentiation of typhus and typhoid	Refs 1 2
General	Refs 1 2 3 4 6
Pathology	Refs 10 13
Therapy antibiotics	Refs 16 17
Therapy para aminobenzoic acid	Ref 15
Transmission by the louse	Refs 7 13
Typhus in the guinea pig	Ref 9
Typhus rickettsia	Ref 12
Weil Felix reaction	Ref 11

Section 16

TYPHUS

ALTHOUGH typhus pretty clearly had existed in jails armies concentrations of people in close quarters and crowded famine areas the nineteenth century was well along before the disease was precisely defined The reasons for this are not far to seek First of all typhus has no very characteristic localizing symptoms or signs except perhaps the rash and this for some peculiar reason was often overlooked or at any rate not mentioned Bartlett (Ref 3) for example tells us that typhus fever is very generally attended with a peculiar and characteristic eruption upon the skin As to the exact frequency of the occurrence of this eruption it is impossible to speak with entire certainty In many cases it has probably been overlooked and besides this it is to be remembered that the diagnosis of typhus fever by many who have written most extensively and most magisterially upon the subject has been anything but rigorous and careful Dr Stewart remarks that the eruption of typhus was unnoticed at Edinburgh until the attention of physicians was called to it by Dr Peebles in 1832 that previous to a visit which Dr Peebles made to the Glasgow Fever Hospital in the spring of 1835 the exanthem of typhus then found to be of general occurrence had neither been looked for nor registered in that institution and was received as a new discovery " (p 207)

Second there were no specific gross lesions at autopsy There was for example nothing to give a definite clue like the characteristic and invariable lesions of the small bowel in typhoid fever The accounts of typhus were therefore vague and consisted of long rambling discussions of fever and prostration such as were typical of eighteenth century medicine James Carmichael Smyth s book (*A Description of the Jail Distemper as It Appeared amongst the Spanish Prisoners at Winchester, in the Year 1780* [London J Johnson 1795]) for example has as its chief claim to distinction that it was written by the father of Thackeray s stepfather Over twenty years later John Armstrong (*Practical Illustrations of Typhus Fever* [2d ed London Baldwin Cradock & Joy 1816]) in his book of over three hundred pages on typhus still dealt largely with vague generalities The terrible epidemics of 1817 1818 and 1819 in Ireland involving hundreds of thousands of cases are dealt with in great detail and in more interesting fashion by F Barker and J Cheyne (*An Account of the Rise Progress and Decline of the Fever Lately Epidemical in Ireland* [2 vols London Baldwin Cradock & Joy 1821]) whose book contains a mine of descriptive material Innumerable case reports are well documented including mention of the exanthem For example "An early eruption of petechiae which were often to be observed on the third or fourth day or even earlier and were visible for four or five days was a general symptom of the disease" (1 454) But no description in any sense modern" preceded the admirable account of Gerhard (Ref 2)

Excellent general discussions of typhus are given by Bartlett (Ref 3) Murchison (Ref 4) and Curschmann (Ref 6) a comprehensive up to-date summary of the whole subject with emphasis on developments in the laboratory is that of J C Snyder (The typhus fevers in T M Rivers *Viral and Rickettsial*

Infections of Man [Philadelphia J B Lippincott Co 1952] p 578) with excellent bibliography Other comprehensive bibliographies are to be found in Curschmann (Ref 6) Murchison (Ref 4) and A Hirsch (*Handbuch der historisch geographischen Pathologie* [2d ed, Stuttgart Ferdinand Enke 1881] 1 385 "Typhus exanthematicus") The book on *Rickettsial Diseases of Man* which consists of various papers read at a symposium in 1946 (Washington D C American Association for the Advancement of Science 1948) contains much interesting material on typhus

An immense amount has been written on the history of typhus Hirsch (*loc cit*) and Murchison (Ref 4) have especially good sections Hans Zinsser s semi popular book (*Rats Lice and History* [Boston Little Brown & Co 1935]) contains much valuable material The story of modern research on typhus is also well summarized by P K Olitsky ("Hans Zinsser and his studies on typhus fever" J A M A 116 907 1941)

1 LOMBARD H C Observations suggested by a comparison of the post mortem appearances produced by typhous fever in Dublin Paris and Geneva (communicated in a letter to Dr Graves) Dublin J M Sc 10:17 1836

Lombard had seen in Geneva and in Paris many patients with typhoid fever and he was quite familiar with the typical lesion of the small intestine What was his surprise when post mortem examinations in Ireland on what was presumably the same disease disclosed no lesions at all of the bowel He finally began to wonder about the identity of the French and Irish "typhus" and while their general similarity was obvious he pointed out certain differences between the two—typhoid fever and typhus "In the first place then the papular or measles like eruption which is always found in our continental typhus [typhoid fever] but which never acquires any great extent or importance is here most remarkable both in appearance and in quantity again in your fever [typhus] this rash is in bad cases mixed with true petechiae and in many of the very malignant ones with purple blotches or *vibices* an occurrence very rare with us

Another symptom which must be considered as constituting a difference is diarrhoea which is much less frequent both before and during typhous fever [typhus] here than it is either in Paris or Geneva In general it seems to me that the abdominal symptoms are less intense and of less importance in this country than with us Another difference I wish to point out is the highly contagious nature of the fever of this country [typhus] compared with that of the continent [typhoid] I can bring forward undeniable proofs of its transmission by contagion but yet its transmissibility from one person to another is far less common with us than it is here"

In a second letter (Second letter from Doctor Lombard to Doctor Graves on the subject of typhous fever" *ibid* p 101) Lombard after having toured the hospitals of England and having crystallized his thinking says "You have two different fevers one highly contagious which I may call the Irish Typhus and in which the cephalic symptoms predominate to the exclusion of abdominal alterations the other which is sporadic [typhoid] and most likely not so infectious and in which the abdominal symptoms are more predominant" Thus the explanation of this perplexity was that there was very little if any typhus

in France or in Geneva whereas in Ireland there was much typhus and in England both typhoid and typhus Anyone seriously interested in the subject must actually read the two letters since here for the first time typhoid and typhus fevers were clearly differentiated

2 GERHARD W W On the typhus fever which occurred at Philadelphia in the spring and summer of 1836 illustrated by clinical observations at the Philadelphia Hospital showing the distinction between this form of disease and dothinenteritis or the typhoid fever with alteration of the *follicles of the small intestine Am J M Sc* 19 289 1836

As a student in Paris Gerhard had become thoroughly familiar with the clinical and pathological features of typhoid fever He knew also that "the typhus fever which is so common throughout the British dominions especially in Ireland, is not attended with ulceration or other lesions of the glands of Peyer He de scribed numerous cases of typhus from the outbreak in Philadelphia in 1836 with careful autopsy reports In a second article (On the typhus which occurred at Philadelphia in the spring and summer of 1836" *ibid* 20 289 1837) Ger hard analyzes the clinical features He gives a good description of the rash of typhus "It consisted of petechiae which in not more than six cases resembled the rose coloured spots of dothinenteritis The petechiae appeared from the sixth to the eighth day after the beginning of the symptoms and disappeared from the fourteenth to the twentieth day There is a marked difference between the petechial eruption and the rose coloured spots of typhoid fever In typhoid fever the eruption is rare very seldom extending beyond the abdo men and thorax whereas in the epidemic typhus the eruption is almost always general extending to the limbs as well as the trunk As to differential diagnosis "When the disease is completely formed the characters on which the distinction between the two forms of fevers rest are (1) The suffusion of the eyes with dusky red aspect of the countenance (2) The extreme stupor and inactiv ity of the mind even when positive delirium does not exist (3) We also observe in typhus no constant abdominal symptom (4) If to these symptoms be added the peculiar eruption of petechiae there remains hardly a possibility of error" Gerhard was sure that the typhus was very contagious

To Gerhard then clearly goes the credit after Lombard, for definitely dis tinguishing typhoid and typhus fevers

3 BARTLETT Elisha The history diagnosis and treatment of typhoid and of typhus fever Philadelphia Lea & Blanchard 1842

Bartlett gives the first worthwhile systematic discussion of typhus There is a minute analysis of symptoms The appearance of the rash "varied from the second to the thirteenth day but in more than half the entire number it appeared on the fifth or sixth day and in three fourths it appeared from the fourth to the seventh day In forty eight cases the eruption began to decline at different periods from the eighth to the nineteenth day" (p 209) In a careful description of the lesions at autopsy one notes the absence of anything specific Bartlett of course could make only crude speculations as to cause "The evi dences of the contagious character of the disease are very positive" (p 231) However the extreme doctrine in regard to the contagiousness of typhus is

that the disease is exclusively and invariably the product of contagion This opinion is not generally entertained, and must have been always the result rather of philosophizing than of observing for certainly the evidence of direct observation is altogether against this exclusive opinion" He thought it certain that the poison of typhus might be generated by "the crowding together in close unventilated apartments amidst accumulations of personal filth of the wretched and suffering poor" (p 236) Under the heading of treatment he discusses bloodletting purgatives affusions and ablutions stimulants and tonics squill, camphor opium and emetics

4 MURCHISON Charles A treatise on the continued fevers of Great Britain 2d ed London Longmans Green & Co 1873

The comprehensive chapter on typhus fever in Murchison s famous book occupies nearly three hundred pages Nonetheless there is really no material advance over Bartlett (Ref 3) a generation before The discussion opens with a definition "A disease generated by overcrowding of human beings with deficient ventilation prevailing in an epidemic form in periods or under circumstances of famine and general destitution and communicable by contagion Its symptoms are More or less sudden invasion marked by rigors or chilliness frequent compressible pulse tongue furred and ultimately dry and brown bowels in most cases constipated skin warm and dry a rubeoloid rash appearing between the fourth and seventh days the spots never appearing in successive crops at first slightly elevated and disappearing on pressure but after the second day persistent and often becoming converted into true petechiae great and early prostration heavy flushed countenance injected conjunctivae wakefulness and obtuseness of the mental faculties followed, at the end of the first week, by delirium which is sometimes acute and noisy but ofttimes low and wandering tendency to stupor and coma tremors subsultus and involuntary evacuations with contracted pupils Duration of the fever from ten to twenty one days usually fourteen In the dead body no specific lesion but hyperemia of all the internal organs softening and disintegration of the heart and voluntary muscles hypostatic congestion of the lungs atrophy of the brain and edema of the pia mater are common"

There follows an excellent and comprehensive section on the history of typhus but the discussion on contagion is especially interesting Murchison like most others at the time was perplexed There seemed to be indubitable evidence of contagion as for example "Persons in comfortable circumstances and living in localities where the disease is unknown are attacked on visiting infected persons at a distance" (p 82) or "Typhus is often imported by infected persons into localities free from it" (p 83) However there also were strong arguments for the generation of the poison *de novo* perplexing at the time but readily intelligible in the light of carriage by a vector Nonetheless the rules for prevention of spread of typhus worked out empirically were effective in practice isolation of patients doing away with overcrowding, bathing patients and destroying their clothes and bedding The section on treatment aside from bloodletting and the "Cold Water Treatment," consists of innumerable drugs and prescriptions which are not worth review

5 MOREAU L and COCHEZ A Contribution à l'etude du typhus exanthematique Gaz hebd de méd 25, 2d ser 388 1888

In the case of practically all febrile diseases the bacteriological era brought attempts to define a living agent as the cause Typhus was no exception and, as early as 1888 Moreau and Cochez working in Algeria isolated from the brain from other organs and finally from the blood and urine of patients a bacillus whose characteristics they describe and which they put forward as the cause of typhus A list of further claims for all sorts of organisms is given in Curschmann's treatise (Ref 6 p 9) Attempts to prove a bacterial cause died hard, however and as late as 1915, the organism of Plotz was widely accepted (Harry Plotz Peter K Olitsky and George Baehr "The etiology of typhus exanthematicus "I Harry Plotz Bacteriologic studies J Infect Dis 17 1 1915 "II Peter K Olitsky Serologic studies ibid p 18 III George Baehr Harry Plotz and Peter K Olitsky Experimental studies" ibid p 40) In elaborate studies Plotz with his associates Olitsky and Baehr isolated an anaerobic bacillus with great constancy from the blood of patients with typhus they found specific serological reactions and isolated the organism from animals which had been inoculated with it They regarded the distemper which they produced in animals as typhus

6 CURSCHMANN, H Das Fleckfieber Vienna Alfred Hölder 1900

This thorough and systematic treatise by a great German clinician emphasizes how little the knowledge of typhus had advanced by the end of the century Curschmann is too close to the old ideas to deny categorically the doctrine of generation *de novo* of the *contagium* However he does say that most current investigators are of the opinion that the *contagium* is contained in the exhalations of the patient in his expired air in the evaporations from his skin etc and that it sticks to dust particles which fill the air surrounding him" This doctrine of course is only a step away from that of miasms There is an admirable clinical analysis of the disease but the pathological descriptions are inadequate and miss what were later (Ref 13) found to be the essential lesions

7 NICOLLE Charles COMTE C and CONSEIL E Transmission experimentale du typhus exanthématique par le pou du corps Compt rend Acad d sc 149 486 1909

Charles Nicolle ("Reproduction expérimentale du typhus exanthematique chez le singe Compt rend Acad d sc 149 157 1909) had already succeeded in infecting monkeys with blood from a typhus patient He concluded that his experiments proved "(1) the possibility of transmitting human typhus to the chimpanzee and after passage through it to the *Macacus sinicus* a common species (2) the presence of the virus in the blood of man on the day of the eruption and in the blood of the chimpanzee 2 days before its appearance" After an incubation period of 25 days a febrile prostrating disorder with rash appeared However monkey typhus has never been suitable for routine experimental work and was promptly superseded by the distemper produced in guinea pigs

Nicolle Comte and Conseil studying typhus in Tunis reasoned that the disease was transmitted by the bite of an insect "Several observed facts have led us to limit our hypothesis to the louse" such as that people bathed and

freshly clothed did not get typhus whereas those who handled the clothes did "we know of two cases in which typhus manifestly followed the bite of a louse" Lice which had been fasted for 8 days were allowed to feed on a monkey which had been inoculated with typhus blood The lice were then applied to other monkeys which in due time came down with "typhus" "These experiments show that exanthematic typhus can be transmitted to the monkey by means of the body louse The application of this finding to the etiology and prophylaxis of the disease in man is imperative" And so it indeed turned out for this work was really the start of the great flood of modern research on typhus Nicolle and his associates soon extended and amplified their original observations in a series of notes (C Nicolle and E Conseil "Reproduction expérimentale du typhus exanthématique chez le macaque par inoculation direct du virus hu main" Compt. rend Acad d. sc 151 258 1910 "Données expérimentale nouvelles sur le typhus exanthématique" *ibid* p 454) and in a long article (Charles Nicolle "Recherches expérimentales sur le typhus exanthématique entreprises à l Institut Pasteur de Tunis pendant l année 1909" Ann Inst Pasteur 24 243 1910 *ibid.* 25 1 1911) Nicolle laid emphasis on the pre ventive and curative properties of sera of convalescent patients and animals

T H Ricketts and R. M Wilder ("The transmission of the typhus fever of Mexico [Tabardillo] by means of the louse [Pediculus vestamenti]" J.A.M.A. 54 1304 1910) confirmed Nicolle s results They were more conservative however and pointed out that the monkey disease consisted mainly of a febrile reaction without rash and that in passage the infection soon died out They demanded and furnished proof therefore that "typhus" really had been produced by louse bite by challenging the animals which had recovered with in jections of "virulent" blood Without exception they remained well and Ricketts and Wilder regarded this immunity test as essential. Ricketts and Wilder ("The etiology of the typhus fever [Tabardillo] of Mexico City a further preliminary report" *ibid* p 1373) soon made a further report Wilder ("The problem of transmission in typhus fever" J Infect Dis 9 9 1911) a little later after Ricketts death from typhus wrote a classical monograph of some ninety pages with bibliography in which he summarized the literature and amplified the reports of his own work with Ricketts In connection with the experimental observations he emphasized the following points Various species of ape were the only animals so far found susceptible Blood for animal inoculation should be drawn from human typhus cases not later than the tenth day of fever The course in the monkey is sufficiently characteristic to enable a positive diagnosis to be made The disease is similar to that in man it has an incubation period of 6–10 days The absence of cultivable organisms in the blood and of anatomi cal lesions is characteristic Leukocytosis is usually observed One attack con fers absolute immunity The virus of typhus is non filterable Typhus can be transmitted to monkeys by the bites of lice and by the introduction into cuta neous scarifications of the intestinal contents of infected lice It is indicated that the infectiousness of the virus is enhanced within the louse Hereditary trans mission of infectivity in the louse is suggested Wilder outlined the salient points of typhus prophylaxis (1) the destruction of lice (2) the extermination of lice found on the bodies clothing or bedding of patients or of contacts and (3) measures to minimize the danger of exposed individuals being bitten by lice

Joseph Goldberger and John F Anderson (The transmission of typhus fever with especial reference to transmission by the head louse [*Pediculus capitis*] " Hygienic Lab Bull 86 [Washington, 1912] p 37) soon confirmed the work of Nicolle and of Ricketts and Wilder on transmission by lice They concluded that "(1) The body louse may become infected with typhus and the virus is transmissible by subcutaneous injection [into monkeys] of the crushed insect or by its bite (2) The head louse may become infected and [the disease] may be transmitted by subcutaneous injection of the crushed insect and also by its bite

8 BRILL Nathan E An acute infectious disease of unknown origin Am J M Sc 139 484 1910

Brill first reported 'his disease" in 1898 (Nathan E Brill "A study of 17 cases of a disease clinically resembling typhoid fever but without the Widal reaction New York M J 67 48 77 1898) but his final description in 1910 was based on 221 cases The patients were seen in New York City they were mostly immigrants from eastern Europe There might be a preliminary period of 3–4 days of malaise but invasion was usually abrupt with chill and intense headache Headache photophobia apathy and prostration increased with the temperature, which rose rapidly and remained continuously high after the first 2–3 days The rash usually appeared about the sixth day first on abdomen and back and then spreading elsewhere The face however was uninvolved The rash was dull red very slightly raised and did not disappear on pressure On about the twelfth day the fever usually dropped rapidly the rash faded and symptoms cleared Convalescence was rapid The spleen was usually palpable the leukocyte count varied usually from 9 000 to 10 000 but might be higher

Brill ("Pathological and experimental data derived from a further study of an acute infectious disease of unknown origin " Am J M Sc 142 196 1918) soon reported further studies Although he suspected the disease of being typhus he was thrown off by his inability to transmit it to monkeys and in fatal cases no characteristic lesions were found Brill s disease aroused great interest among doctors, and discussions were lively as to its nature

The studies of J F Anderson and J Goldberger ("The relation of so called Brill s disease to typhus fever an experimental demonstration of their identity" Hygienic Lab Bull No 86 [1912] p 25) however showed that Brill s disease could be transmitted to monkeys which were then immune to a subsequent infection with virulent blood of the same strain and were also immune to infection with blood from Mexican typhus Monkeys recovered from an infection with Mexican typhus fever were found immune to subsequent infection with material from "Brill s" disease Hence the writers concluded that European typhus (Brill s disease) and Mexican typhus were one and the same disease H Zinsser ("The varieties of typhus virus and the epidemiology of the American form of European typhus fever [Brill s disease] Am J Hyg 20 513 1934) pointed out that, whereas the strains of virus producing the two forms of typhus were closely related they were not identical They might be regarded as "slightly divergent variants of the same stock." He concluded further that cases of Brill s disease represented recrudescences of old infections originally acquired in European foci which in louse-infected communities might give rise to new epidemic outbreaks

9 NICOLLE Charles CONSEIL E and CONOR A Le Typhus expérimental du cobaye Compt rend Acad d sc 152:1632 1911

"When one inoculates several guinea pigs with variable quantities (8 6 4 3 2 cc.) of blood from a typhus patient, some of the animals die in a few days with loss of weight and hypothermia these are the ones which receive the larger doses The others contrariwise inoculated with smaller amounts show no apparent symptoms—at the most a transient loss of weight. However if one takes the temperature of these guinea pigs which show nothing objectively one finds that in certain animals not in all there is a fever for several days comparable to that which is shown by monkeys inoculated with the same blood and with more overt typhus" The specificity of this reaction was soon confirmed by others John F Anderson ("The reaction of the guinea pig to the virus of typhus fever" J M Research 30 467 1914) found that many guinea pigs had a natural immunity to a first injection of typhus blood from human cases although only 4 7 per cent failed to react to an inoculation of virulent guinea pig typhus blood

However this test has become a standard procedure in typhus work and it was depended upon by Wolbach Todd and Palfrey (Ref 13) in their important studies in the Polish epidemic in 1920 They review the literature[1] and give a comprehensive account of the clinical and pathological features of the guinea pig disease P K Olitsky ("Definition of experimental typhus fever in guinea pigs" J A M.A 78 571 1922) defines the guinea pig disease precisely and the subject is also reviewed by John C Snyder ("The typhus fevers" in Rivers *op cit* p 587)

10 FRAENKEL, Eugen Ueber Fleckfieber und Roseola Munchen med Wchnschr 61 57 1914

It occurred to Fraenkel to seek the causal agent of typhus in the skin lesions He excised bits of the exanthematous skin without anesthesia and fixed and stained the material He described a lesion quite different from that found in the rose spots of typhoid fever he found thickenings of the walls of small vessels which were due "to infiltration not with leukocytes but with mononuclear cells" He described these cells in detail and also changes in the vessel wall He decided that "in fact a peculiar lesion of the small arteries is the essential feature of the skin lesion" and he concluded by suggesting that similar lesions might be found in internal organs In a later paper Fraenkel ("Zur Fleckfieberdiagnose" *ibid* 62 805 1915) gave a further description and noted that one saw "swelling and necrosis of the intima and marked swelling of the adventitial and periadventitial cells" Fraenkel regarded the lesions as specific and capable of giving a definite diagnosis His work was soon confirmed and changes were described in various internal organs The extensive literature is reviewed in Wolbach Todd and Palfrey's report (Ref 13) and the general subject of the pathology of typhus is considered in the elaborate monograph by W Ceelen ("Die pathologische Anatomie des Fleckfiebers" in *Ergebn d allg Path u path Anat*

[1] Curiously enough these writers refer to the 1909 paper of Nicolle Comte and Conseil (Ref 7) and to the 1910 papers of Ricketts and Wilder (Ref 7) as first showing the susceptibility of the guinea pig Actually these papers deal only with monkeys and the first reference to guinea pigs is the 1911 paper of Nicolle Conseil and Conor (Ref 9)

[Wiesbaden 1919] p 307) which contains a comprehensive bibliography Wolbach Todd and Palfrey (Ref 13) give a minute account of the lesions and picture beautifully masses of *Rickettsia* in the cells of blood vessel walls An authoritative summary of the subject is also given by S Burt Wolbach in "The pathology of the rickettsial diseases of man in *Rickettsial Diseases of Man* (Washington American Association for the Advancement of Science 1948) p 118

11 WEIL E and FELIX A Zur serologischen Diagnose des Fleckfiebers Wien klin Wchnschr 29 33 1916

Weil and Felix in the course of examining cultures from typhus patients grew from the urine of V a Rumanian physician a micro-organism which was not agglutinated by sera from typhoid paratyphoid A and B or dysentery cases It was however agglutinated by the patient s own serum in a dilution of 1 200 The organism turned out to be a Gram negative bacillus Tested with typhus sera it was agglutinated in all of thirty three cases in dilutions of 1 25 to 1 500 The agglutinins reached their peak at the time the eruption appeared remained up about 14 days and then fell rapidly Weil and Felix concluded that "in this bacterium we have found an aid in diagnosis of typhus A little later Felix (Die Serodiagnostik des Fleckfiebers *ibid* p 873) pointed out that the two strains isolated by Weil and Felix (X_1 and X_2) were being widely used in the diagnosis of typhus Weil and Felix soon isolated another strain from urine of a typhus patient (X_{19}) which made the diagnosis of typhus much easier and more certain " Felix concluded "The highly specific agglutination reaction with X_{19} occurs earlier and in higher dilution than with the previously used strain X "

We cannot review the immense amount of work subsequently done on this subject but refer the reader to Kenneth Wertman s review ("The Weil Felix re action " in *Rickettsial Diseases of Man* p 184) In the same monograph C J D Zarafonetis ("The serological reactions in the rickettsial diseases of man" p 178) and Joseph E Smadel ("Complement fixation and agglutination reac tions in rickettsial diseases p 190) review the whole subject of serological reactions in typhus with bibliographies

12 DA ROCHA LIMA H Beobachtungen bei Flecktyphuslausen Arch f Schiffs u Tropen Hyg 20 17 1916

Going on the presumption "no lice no typhus fever " Da Rocha Lima sought a causal agent in the louse "In the first smears from infected lice I was struck by a prodigious number of bacillus like bodies which stained pinkish with Giemsa s stain " These were obviously not normal constituents of the louse since they were absent in controls They were found chiefly in the alimentary canal It was not possible to grow them on the ordinary bacteriological media Da Rocha Lima succeeded in infecting guinea pigs with minute amounts of suspen sions of intestinal contents The organisms" were also present in the salivary glands Whether these were the bodies seen by Ricketts and Wilder (Ref 7) and by S von Prowazek ("Aetiologische Untersuchungen uber den Flecktyphus in Serbien 1913 und Hamburg 1914 Beitr z Klin der Infectionskr 3 5 1914) is uncertain Both Ricketts and Von Prowazek died of typhus in the course of their investigations Da Rocha Lima s definitive paper (Zur Atiologie

des Fleckfiebers" Centralbl f allg Path u path Anat 1916 Beiheft zu Band 27 p 45 1916) soon appeared in which he made a definite claim for his organism as the cause of typhus and gave it the name of *Rickettsia prowazeki* in honor of the investigators who succumbed to the disease He now demonstrated and pictured the organisms in the epithelial cells of the alimentary tract in which "a lively multiplication takes place and only in a narrow zone of protoplasm near the nucleus" He again showed a regular coincidence of *Rickettsia* in the louse with its infectivity for guinea pigs Various other time and temperature relationships were worked out. In a later paper (F Munk and H da Rocha Lima "Klinik und Aetiologie des sogen 'Wolhynischen Fiebers [Werner Hissche Krankheit]" H H da Rocha Lima "Ergebnis der atiologischen Untersuchungen und deren Beziehungen zur Fleckfieberforschung," Munchen med Wchnschr 64 1422 1917) Da Rocha Lima fortified his previous conclusions and distinguished *Rickettsia prowazeki* from other similar organisms in diseased and healthy lice The definitive observations of Wolbach Todd and Palfrey (Ref 13) however settled to the satisfaction of everyone the role of *Rickettsia* as the cause of typhus H Plotz J E Smadel T F Anderson and L A Chambers ("Morphological structure of *Rickettsia*" J Exper Med 77 355 1943) studied and pictured the appearance and structure of *Rickettsia* as revealed by the electron microscope

13 WOLBACH S Burt TODD John L and PALFREY Francis W The etiology and pathology of typhus Cambridge Mass Harvard University Press 1922

This volume a landmark in the history of the subject represents work done by a commission sent to Poland in 1920 to study typhus As the writers say in their Introduction they amplified and consolidated rather than made fundamentally new discoveries Thus they improved the methods of collecting caring for and feeding lice they made very careful clinical studies they proved beyond question the specificity of *Rickettsia prowazeki* for typhus by having *Rickettsia* free lice feed on typhus patients and then producing the disease in guinea pigs by inoculation of infected louse viscera they made definitive studies of the guinea pig disease and its pathological anatomy and they studied with the greatest care and pictured the pathology of typhus in man They conclude that typhus is a disease of small blood vessels and that the parasite localizes almost exclusively in the vascular endothelium "The reaction to the parasite is shown primarily by degenerative changes giving rise to thromboses in blood vessels and by a proliferative reaction on the part of endothelium [p 200] As there is no specific stain for *Rickettsia prowazeki* the following criteria must be satisfied (1) the size (2) morphology (3) staining reactions must correspond with those of *Rickettsia prowazeki* in sections of lice and (4) they must be present in vascular endothelial cells *in situ* in relation to the lesions of typhus

14 COX Herald R and BELL E John Epidemic and endemic typhus protective value for guinea pigs of vaccines prepared from infected tissues of the developing chick embryo Pub Health Rep 55 110 1940

Cox ("The preparation and standardization of rickettsial vaccines" in *Rickettsial Diseases of Man* p 203) reviews the long story of the development of vaccines against typhus He tells how living and attenuated live vaccines turned

out to be dangerous and the difficulties of obtaining sufficient quantities of *Rickettsia* from lice for commercial use of killed vaccine It was the development by Cox (Use of yolk sac of developing chick embryo as medium for growing *Rickettsia* of Rocky Mountain spotted fever and typhus groups" Pub Health Rep 53 2241, 1938) of a method for growing *Rickettsia* in large numbers which solved the problem From infected tissues of developing chick embryos Cox and Bell prepared vaccines that will protect most of the test guinea pigs against epidemic (European) typhus Mass production methods were soon developed R S Ecke *et al* ("The effect of Cox type vaccine on louse borne typhus fever Am J Trop Med 25 447 1945) found that while typhus did occur in the vaccinated the course was milder and only an occasional patient died A G Gilliam (Efficacy of Cox type vaccine in the prevention of naturally acquired louse borne typhus fever Am J Hyg 44 401 1946) came to somewhat similar conclusions Finally J F Sadusk Jr ("Typhus fever in the United States Army following immunization incidence severity of disease modification of clinical course and serological diagnosis" J A M A 133 1192 1947) discussed the extensive army experience From January 1942 to December 1945 only 64 cases of epidemic typhus occurred in the armed forces Sadusk feels that while the incidence may not be reduced the severity of attack is much diminished and mortality practically eliminated

15 YOUNGMANS A SNYDER J C MURRAY E S ZARAFONETIS C J D and ECKE R S The therapeutic effect of para aminobenzoic acid in louse borne typhus J A M.A 126 349 1944

These workers first described beneficial effects from large doses of para aminobenzoic acid in louse borne typhus if treatment was started in the first week of illness J C Snyder *et al* ("Further observations on the treatment of typhus with para aminobenzoic acid" Ann Int Med 27 1 1947) reported further on the curative action of this drug in typhus They give details of administration and emphasize the importance of starting the treatment early and of "attaining promptly and maintaining a concentration of the drug in the blood above 10 mg per 100 cc for *R prowazeki*" However at present (1952) one of the wide spectrum antibiotics (Refs 16 17) is considered the drug treatment of choice (J C Snyder in Rivers *op cit* p 595)

16 WONG Sam C and COX Herald R Action of aureomycin against experimental rickettsial and viral infections Ann New York Acad Sc 51 290 1948

Wong and Cox found that aureomycin possessed marked therapeutic activity against the virus of typhus in embryonated hen s eggs mice and guinea pigs Guinea pigs receiving massive doses of virus were protected by aureomycin, if the drug was given very early against any symptoms but the animals developed no antibodies With small doses of virus aureomycin protects against symptoms and the animals develop no antibodies nor are they immune "These findings indicate a quantitative relationship between the dosage of infecting agent and the dosage and time of administration of aureomycin" Soon after J C Snyder *et al* ("Experimental studies on the antirickettsial properties of terramycin" Ann New York Acad. Sc 53:362 1953) found that terramycin has antirickettsial properties against *R prowazeki* in chick embryos and mice and finally

J E Smadel and E B Jackson ("Chloromycetin an antibiotic with dermotherapeutic activity in experimental rickettsial and viral infections" Science 106:418 1947) found chloramphenicol effective in R *prowazeki* infections of eggs and of mice

17 SMADEL, J E LEON A P LEY H L and VARELA G Chloromycetin in the treatment of patients with typhus fever Proc Soc Exper Biol & Med. 68:12 1948

The experimental work on the newer antibiotics in egg and guinea pig infections with typhus virus (Ref 16) were soon followed by trials in man Smadel and his group obtained favorable results in a few patients treated with chloromycetin by mouth E H Payne E A Sharp and J A. Knaudt ("Treatment of epidemic typhus with chloromycetin" Tr Roy Soc Trop Med. & Hyg 42 163 1948) soon reported the treatment of twenty two patients with the same drug both intravenously and orally "The favorable effects of treating typhus (epidemic) with chloromycetin appear rapidly and the patient usually enters convalescence within 3 days" A little later E B Schoenbach ("Aureomycin therapy of recrudescent epidemic typhus [Brill's disease]" J A.M.A 139 450 1949) reported a case of typhus treated on the sixth day with aureomycin by oral and intramuscular routes with prompt clinical improvement.

Thus the experimental results seem to be confirmed in man

18 Control of communicable diseases in man An official report of the American Public Health Association p 203 1955

In this outline are given in detail authoritative directions for prevention of epidemic (louse-borne) typhus indicating the use of insecticides delousing immunization etc The technique of prevention is also well discussed with graphic illustrations in War Department Technical Bulletin (TB Med No 218) *Epidemic (Louse borne) Typhus* (Washington April 17 1946)

SYPHILIS PART I FROM JOHN HUNTER TO DISCOVERY OF THE TREPONEME (1905)

Aneurysm	Ref 30
Bismuth	Ref 36
Clinical and general	Refs 1 2 3 5 7 11 12 17 19 22 24 26 40
Congenital	Refs 3 11 16 27 35
Discovery of spirochete	Ref 43
Hutchinson s teeth	Ref 23
Incubation period	Refs 13 22 27
Inoculation	Refs 10 12 18 19 22
Iodide	Ref 9
Paresis	Ref 31
Pathology	Refs 20 25 33
Syphilis of nervous system	Refs 21 28 37 43
Syphilis and public health	Refs 34 41
Syphilitic aortitis	Ref 39
Tabes dorsalis	Refs 14 29 32
Transmission to animals	Ref 42
Treatment	Refs 6 7 11 12

SYPHILIS PART I

IT IS not our purpose to take up in this bibliography the vast literature on the history of syphilis For this phase of the subject the reader may be referred to such scholarly works as those of Iwan Bloch (*Der Ursprung der Syphilis* [Jena Gustav Fischer Part I 1901 Part II 1911]) of Gaston Vorberg (*Ueber den Ursprung der Syphilis* [Stuttgart Julius Puttman 1924]) and of Karl Sudhoff (*Aus der Fruhgeschichte der Syphilis* [Leipzig J Barth 1912]) An excellent brief account in English is that of William Allen Pusey (*The History and Epidemiology of Syphilis* [Springfield Charles C Thomas 1933])

We shall begin rather with John Hunter in the late eighteenth century and attempt to give in this instalment the key references which trace the development of the subject until the discovery of the spirochete The problem is difficult because nearly everyone of importance who wrote on syphilis produced a large book mostly copied from previous writers in which lay buried a few grains of new knowledge However one can trace from Hunters primitive ideas on the identity of gonorrhea chancroid and syphilis a gradual realization by astute clinical observation and by inoculation and confrontation experiments that these were three different diseases Along with this came more accurate classification of the clinical stages of syphilis the timing of the incubation period and study of the anatomy of the lesions We shall trace the realization which gradually dawned in the last quarter of the nineteenth century of the role of syphilis in tabes and paresis and in aneurysm One marvels how clinicians unarmed with knowledge of the spirochete without the Wassermann reaction and without spinal fluid examination were able to detect these relationships at all On the whole though things moved very slowly and practically no advance in treatment was made until the discovery of the arsphenamines

It is impossible to begin to list even all the major titles we have tried to select books or articles in which an outstanding contribution was made For detailed bibliography one should refer to the monumental work of J K Proksch (*Die Literatur uber die venerischen Krankheiten* [3 vols Bonn Peter Hanstein 1889–1900])

1 HUNTER John A treatise on the venereal disease London 1786 (Numerous editions during the next fifty years We quote from the first American edition [Philadelphia Parry Hall 1791])

Modern discussion of syphilis may be said to begin with John Hunter Hunters great name and reputation were so influential that his work dominated the field for decades and few dared write on venereal disease without deferring, or at least referring to him His book ran through many editions and was translated into French and German Actually Hunter confused and held back the subject for two generations Great as he was as a surgeon his observations and ideas on syphilis were hopelessly inadequate He accepted a preconceived doctrine that two different diseases could not coexist in a patient (it appears to me beyond a doubt, that no two actions can take place in the same constitution nor in the same part at one and the same time [p 2]) and consequently he believed

that there was only one venereal disease which manifested itself in three ways as gonorrhea chancre or lues venerea Whether the first manifestation was a gonorrhea or a chancre depended Hunter thought on the type of surface upon which the poison fell In addition he believed correctly that there were many non specific (syphiloid) genital ulcers which could be mistaken for the true venereal disease Often the test of whether the lesion disappeared under mer cury was the only way he claimed of identifying syphilis

"A chancre has commonly a thickened base said Hunter (p 195) but on the whole his description is not at all precise So too as to incubation period Hunter stated that on the whole the chancre "is rather longer in appearing than gonorrhea" (p 198) but he gave the time as 24 hours to several weeks Hunter thought the surest method of treating a chancre was by destruction or excision (p 208) and that if this was done promptly there was but "little danger of the constitution being infected" (p 209) But as one could not be certain "it would be prudent to give some mercury internally as well" (p 209) And later "In every case of a chancre let it be ever so slight mercury should be given internally even in those cases where they were destroyed on their first appearance It should in all cases be given the whole time of the cure and con tinued for some time after the chancres are healed for as there are perhaps few chancres without absorption of the matter it becomes absolutely necessary to give mercury to act internally in order to hinder the venereal disposition from forming" (p 219) Here Hunter was certainly sound "The immediate consequence of the local diseases gonorrhea and chancre which is called bubo as also the remote or lues venerea arise from the absorption of recent venereal matter" (p 231)

We are especially concerned with Part VI chapter i "Of the Lues Venerea" This Hunter called "the constitutional part of venereal disease" in consequence of the poisonous matter being absorbed (p 262) From this point on however his description of later lesions is for the most part obscure inadequate and based on a fanciful theory of the whole situation although he had some idea of the stages of syphilis "The parts that are affected by this form of the disease when in its early stage or appearance which I have called first in order are the skin tonsils nose inside of the mouth and sometimes the tongue When in its later state the periosteum fasciae and bones come into action and these I call second in order of parts" (p 281) But he by no means really differentiated secondary and tertiary lesions

"Mercury in the lues venerea as in the chancre is the great specific and hardly anything else is to be depended upon" (p 307) said Hunter and then he continued with a long discussion of preparations quantity and mode of administration with a *description of their actions and effects* It *is* easy to see how hopeless accurate evaluation of any therapeutic agent in syphilis had to be until much more was known about the fundamentals of the disease

John Hunter was essentially a practical man He did badly in school and never learned Latin or Greek at that time considered essential for a gentleman s education He got into medicine by way of his beautiful anatomical dissections and undoubtedly became a skilled and resourceful surgeon His very precision in making observations however seems to have interfered as it sometimes did in the case of the great Virchow with sound reasoning Hunter thought in terms

of humors his medical outlook was oriented to the past rather than to the newer points of view so well emphasized by the brilliant French clinician pathologists

Hunter's confused ideas about syphilis and venereal disease in general may be brought out by a few quotations from his book

I divide sympathy into two kinds universal and partial"

Universal sympathy is an infection wherein the whole constitution sympathizes with some sensation or action Partial sympathy is an infection wherein one or more distinct parts sympathize with some local sensation or action (p 11)

The following case is an instance of a gonorrhoea producing a lues venerea To account for these two very different effects of the same poison it is only necessary to observe the difference in the mode of action of the parts affected when irritated let the irritation be what it may The poison then being the same in both cases why do they not always happen together in the same person? For one would naturally suppose that the gonorrhoea when it has appeared, can not fail to become the cause of a chancre and that this when it happens first must produce a gonorrhoea (p 16) "The venereal disease also becomes often the immediate cause of other disorders by calling forth latent tendencies to action This does not happen from its being venereal but from its having destroyed the natural actions so that the moment the venereal action and disposition is terminated the other takes place (p 24) "It has been observed before that there are three forms of the venereal infection gonorrhoea chancre and the lues venerea which various forms I have endeavoured to account for As they all three arise from the same poison and as the two first depend only on a difference in the nature of the parts and the lues venerea on another circumstance which has been explained it would be natural to suppose that one medicine whatever it be would cure all forms of this disease But we find from experience that this does not hold good for one medicine that is mercury cures only the chancre and the lues venerea and the gonorrhoea is not the least affected by it (p 304) Apparently this observation did not suggest to Hunter that gonorrhea was a distinct disease In other passages some of which we have quoted above Hunter seemed to sense dark glimmerings of the truth

The overwhelming evidence of contact as a precursor of syphilis led Hunter and physicians generally to believe that the poison of the disease was communicable from person to person Hence students of venereal disease for several decades centered their attention on (1) the clinical differentiation of the various venereal lesions (2) attempts to distinguish them by inoculation of their products into the skin or genital organs of the same people or occasionally of others (3) an analysis of the sequence of events i e relation of primary to later lesions and (4) the question of whether mercury was necessary for the cure of syphilis and if so how the drug should be used

2 BELL Benjamin A treatise on gonorrhoea virulenta and lues venerea 2 vols Edinburgh James Watson & Co 1793

Bell was the first clearly to differentiate gonorrhea from syphilis The opinion which I have ventured to support of the difference between the matter of Gonorrhoea and that of Lues Venerea will no doubt be censured by many"

(1:x) "It is well known that Lues Venerea can certainly be cured by mercury only and the opinion respecting the existence of a specific contagion of Gonorrhoea arising from this obvious and marked difference in the method of cure appears to be fixed and established by the following facts The symptoms and consequences of Gonorrhoea are perfectly different from those which take place in Lues Venerea Both diseases have appeared at different periods in the same countries and in some instances have remained distinct and uncombined for a great length of time" (1 2) "That the symptoms of the two diseases are different is universally known A particular detail of such as are peculiar to each will be given in the ensuing chapters At present Gonorrhoea is admitted to be in almost every instance a local affection and it very rarely con taminates the general habit of body while Lues Venerea is a disease of the constitution arising from the absorption of venereal virus from any part of the surface of the body but most frequently from the genitals (1 3)

Although this was written shortly after Hunter s first edition few seemed to pay attention until Bell s opinion was reaffirmed by Hernandez (Ref 4) and on the basis of inoculation experiments by Ricord (Ref 12) The story of this controversy is well told and documented in Rollet s book (Ref 22 p 70)

In Volume 2 Bell gives a clear and readable account of syphilis far superior we think to Hunter s When Lues Venerea is not interrupted in its progress by the use of mercury or other remedies the following is the order in which the symptoms commonly appear viz chancres buboes ulcers and inflammation of the throat ulcers in the mouth and nose eruptions or blotches on the surface of the body ulcers in different parts nodes and swellings in the periosteum bones and tendons excrescences about the anus swellings of the testes loss of hair from all parts of the body blindness loss of hearing and other anomalous symptoms" (2 12) Bell probably confused "soft chancre" with syphilitic pri mary lesion since he speaks of it as often appearing almost immediately after contact

Half of Volume 2 is devoted to therapy One of the most certain effects of mercury is that it acts as a cure for venereal disease" (2 185) There is a long discussion of just how mercury should be used and at what time "The preparations of mercury are very numeous upwards of five hundred might be enumerated" (p 215) The problems of the toxic effects of mercury are dis cussed and the fact that inadequate therapy might be followed by severe later symptoms led to the usual confusion in its use As late as 1839 one even finds a book entitled *Practical Observations Showing that Mercury Is the Sole Cause of What Are Termed Secondary Symptoms* by P J Murphy (London John Churchill 1839)

3 BERTIN M Traité de la maladie vénénenne chez les enfants nouveau nés les femmes enceintes et les nourrices etc Paris Gabon 1810

Bertin s book was recognized by the Academy of Medicine of Paris as of great importance because his work was based on personal observation of a large number of patients This seems to be the first systematic treatise on congenital syphilis It begins with a critical chapter on previous work Bertin then out lines the methods whereby congenital syphilis is acquired He believes that there are three infection of the fetus at the time of conception infection during gestation and infection during passage through the birth canal The clinical de-

scriptions of congenital syphilis are inadequate from the modern standpoint but each manifestation is documented by a number of case reports Chapter xvi on the treatment of pregnant women is of special interest "In treating the pregnant woman one often cures the mother and child at the same time if the mother *is* not admitted too far along in her pregnancy" The backbone of therapy was mercury by inunction or by mouth the details of administration are discussed at great length This book with all its inadequacies is a definite landmark in the study of congenital syphilis

4 HERNANDEZ J F Essai analytique sur la non identité des virus gonorrhoique et syphilitique Paris J J Paschoud 1812

This book was crowned" by the Société de Médecine of Bezançon for work on the following question 'To determine by experiment and conclusive observation whether there is an identity of the virus of gonorrhoea and of syphilis whether one can give rise to the other and whether the treatment suitable for one applies to the other These questions Hernandez answers systematically in chapters headed as follows Gonorrheal Infection Always Has Gonorrhea for an Effect and Never a Chancre 'Gonorrheal Infection Always Gives Rise to Gonorrhea , "Gonorrhea Occurs without Chancre or Syphilitic Ulcer in the Urethra" 'The Virus of Gonorrhea Does Not Produce Chancre etc The argument is inexorably followed through the book of 350 pages

5 SCHMIDT Johann Adam Vorlesungen uber die syphilitische Krankheit und ihre Gestalten Vienna Bey Kupfter & Wimmer 1812

This little book may be mentioned as an example of the state of knowledge about syphilis in Germany in the early nineteenth century The author leans heavily on Hunter He recognizes the incubation period before the chancre and the second incubation period before generalized manifestations However he confuses "tripper" and chancre again following Hunter There are dark gropings to extract from clinical observations some rules about the progress of the disease and "clinical immunology There is of course no allusion to cardiovascular or nervous system syphilis Half the book deals with the "ins and outs" of mercurial therapy which at the time was elevated almost to a discipline of its own

6 CARMICHAEL Richard Observations on the symptoms and the specific distinctions of venereal diseases interspersed with hints for the more effectual prosecution of the present enquiry into the uses and abuses of mercury in their treatment London Longman Hurst Rees Orme & Brown 1818

This book is important first because Carmichael strongly supported Bell as regards the distinction of syphilis and gonorrhea (p 5) and also because he was a prominent figure in the current dispute as to whether mercury was advisable at all in the therapy of syphilis The toxic effects of heavy mercurial treatment were often obvious and some thought that the late symptoms of syphilis might be due to mercury (Ref 2) "With respect to the material point in the present investigation my experience enables me decidedly to affirm that if the papular eruption or its accompanying symptoms do not return in a patient *who has not used mercury* after a lapse of a few weeks he may be considered

as perfectly well but on the contrary *if he has employed that medicine* the dis order may return after an interval of many months" (p 22)

This observation becomes clear in the light of modern immunological knowl edge of syphilis

7 BACOT John A treatise of syphilis in which the history symptoms and methods of treating every form of that disease are fully considered London Longman Hurst, Rees Orme & Brown 1829

This valuable book begins with a critical summary of contemporary views on the venereal disease problem The opening chapters give a comprehensive review of the history of syphilis and the third, of special importance is entitled "Modern Doctrines of Syphilis Examined" Here contemporary views beginning with Hunter are carefully analyzed and compared The upshot of all this is that there was great uncertainty in the classification of venereal disease and that syphilis and gonorrhea were usually considered due to the same poison The primary lesion was recognized but was obviously often confused with non syphilitic phagedenic and pyogenic ulcers So too the bubo was accepted as a satellite of the primary lesion but the frequency of suppuration indicates that other than syphilitic glandular swellings might be present The later lesions were skin eruptions sores in the throat bone lesions especially of the palate nose and cranium and iritis No hint of cardiovascular or nervous system syphilis is given in fact the author states "There is no reason to believe that the viscera are ever subject to the attacks of syphilis" (p 82)

The usual bitter discussions of just how mercury should be used and to what extent it is specific are critically gone into "It is vain to attempt to form any rational theory as to the mode in which mercury operates in the cure of syphilis to relate all the strange imaginations that ingenious men have thought fit to make public on this subject would only waste our time If mercury cannot be called a specific in the cure of this disease it at least approaches as nearly to that character as any medicine can be said to do in any complaint whatsoever" (p 256) Of special importance was the question which was raised at the time of whether mercurial treatment was of any value at all and whether patients did not do just as well with no "specific therapy" During the Peninsular Wars English physicians learned that the Portuguese got good results with no special therapy and Mr Rose an army surgeon returning from Portugal (p 49) "adopted the only rational plan—that of putting the question to the test of experiment discarding all preconceived notions and looking solely at the natural progress of the disease itself The results of these experiments made in the hospital of the Coldstream regiment of guards were given to the world in 1817 ("Observations on the treatment of syphilis with an account of several cases of that disease in which a cure was effected without the use of mercury by Thomas Rose Esq A M " M Chir Tr 8 349 1817 also "Observations on the treatment of the venereal disease without mercury" by G J Guthrie Esq M Chir Tr 8:550 1817 see also Carmichael [Ref 6]) Mr Rose found that he could cure all genital ulcers" without mercury and he as well as many other observers then followed the patients for the incidence of secondary manifestations These were less common in those treated with mercury but most of the patients seemed to remain well although they really were not followed long

enough to prove anything by modern standards These early purposeful experiments are of interest in view of the modern observations of Bruusgaard and others

The usual perplexities of syphilitic children being born of apparently healthy mothers are encountered

The book is so full of important and interesting material that complete review would be unduly long, no serious student of syphilis however should fail to study it in detail

8 HACKER Heinrich August Literatur der syphilitischen Krankheiten von Jahre 1794 bis mit 1829 Leipzig J F Gleditsch 1830

This invaluable bibliography contains nearly a thousand references After each there is a brief paragraph giving the substance of the material The book seems essential for any intensive study of the period (Hacker later continued his bibliography *Neueste Literatur der syphilitischen Krankheiten* [vom 1830–1838] *nebst Nachtragen zu fruheren Jahren* [Leipzig 1839])

9 [Dr WALLACE] Hydriodate of potash in syphilis Lancet, 1 743 1836

Wallace refers to 124 cases of "secondary syphilis which he treated with potassium iodide *with great success When first admitted he kept the ward awake* all night by his roaring out with the agonizing pains in his bones he says he now rests comfortably

This is said to be the first claim for benefit from iodide in syphilis although according to Lancereux (Ref 26) there were some preliminary attempts by Lugol and others Lancereux (Ref 26 p 700) also summarizes the prompt confirmation of the value of iodides by numerous other workers See also William Wallace "Treatment of the venereal disease by the hydriodate of potash or iodide of potassium" Lancet 2 5 1836

10 WALLACE [William] Clinical lectures and remarks delivered on diseases of the skin venereal disease and surgical cases at the skin infirmary and at the Jervis Street Hospital Dublin Lancet 2 534 615 1836–37

To Wallace are attributed the first purposeful observation on inoculation of material from various syphilitic lesions into healthy people A scrutiny of the experiments leaves one however somewhat dissatisfied The cuticle was removed by friction from an area the size of a shilling and material from the syphilitic lesion was applied on a piece of lint Variable responses occurred but in some of the cases after initial infection and healing later breakdown again took place "The local specific effects which result from the inoculation with the matter of the primary pustule and of the pustular bubo commence almost immediately The local specific effects which result from inoculation with the matter of secondary pustule as well as with the matter of the different varieties of exanthematic syphilis do not occur for some weeks after inoculation" In Berkeley Hill s book (*Syphilis and Local Contagious Disorders* [London James Walton 1868]) is found (p 62) a table of thirty more cases of experimental inoculation of syphilis which the writer found acceptable How confused this branch of the subject became may be guessed from the book by Heinrich Auspitz (*Die Lehre vom syphilitischen Contagium* [Vienna W Braumuller

1866]) in which all the inoculation experiments in the literature are quoted and analyzed

11 COLLES Abraham Practical observations on the venereal disease and on the use of mercury London Sherwood Gilbert & Piper 1837

While this work is known mainly for the observations on congenital syphilis (see below) which at the present time are usually formulated as Colles law it presents many other phases of syphilis of equal interest and importance Colles primary object was a defense of mercurial therapy—a procedure long in use but at the time in disfavor in some quarters—but incidentally there are taken up various clinical and immunological aspects of the disease Colles gives credit to Hunter (Ref 1) for first clearly recognizing the orderly temporal relationships of the manifestations of syphilis but he realizes that only a beginning has been made in the study of the natural history of the disease Difficulties still encountered today—namely that patients do not stay under the observation of the same physician during their entire course and that the clinical picture is soon modified by treatment—are pointed out and the need for group study is stressed However the descriptions of primary lesions both genital and extra genital the various eruptions the lesions of the mucous membranes and of bone and especially the congenital manifestations are outstanding "Modern writers on the venereal disease have bestowed much pains in observing and arranging in a nosological order the varieties of cutaneous eruptions which form a part of secondary syphilis I should think the subject might still deserve a continuance of that zeal were I convinced that each form of these eruptions constituted a distinct species in the disease I fear however that any superstructure raised upon this hypothesis will not stand the test of time as I do not believe that these eruptions can be considered as characteristic of distinct and different forms of syphilis" (p 175)

Colles devoted himself to a lesser extent than many of the contemporary writers to attempts to demonstrate the contagiousness and autoinoculability of syphilis He reports observations which clearly show however that secondary as well as primary sores are infectious and further that people who apparently have been cured of the disease and who present no clinical manifestations may nonetheless infect their marital partners and produce syphilitic children " As long as such cases were confined to mechanics and persons in an humble rank of life I could not bring myself to believe implicitly in their reports but when I found some occurring in the higher walks of life and when the husbands proved to be men of acknowledged and known veracity I could no longer withhold my assent [p 263] But there are cases in which the foetus in utero has been infected under circumstances so strange and so difficult to explain that nothing short of actual observation could induce us to allow the fact The circumstances to which I allude are these —The father of the child has had primary symptoms six or eight months before his marriage for these he has been treated by mercury and his surgeon has dismissed him as perfectly cured" Syphilitic children are born although 'both parents continue all this time to live in the enjoyment of perfect health no trace of disease is to be discovered in either" (p 266)

The discussion of therapy is of especial interest because of incidental observations on immunity most of which have been substantiated a hundred years

later by experimental methods Colles recognized the futility of trying to eradicate the disease by local treatment of the chancre "I have known a chancre completely cut out on the first or second day after its appearance yet the occurrence of secondary symptoms was not prevented" (p 77) He also noted that inguinal bubo was not a barrier to the spread of the disease (p 98) Of particular importance are the observations on modification of the course of syphilis by treatment and especially the recognition that inadequate therapy might be followed by violent symptoms "Too frequently are the powers of the constitution so lowered by this indiscriminate use of mercury that it is no longer able as it were to exhibit the eruptive fever but it seems to be prematurely sunk into that weakened state which attends the latest stages of Syphilis" (p 6) " And yet at this day it must be admitted that many cases have resisted its use [mercury] —and further that often where it did not cure it considerably aggravated the sufferings of the patients (p 321) *When we inquire into the time at which the secondary disease has succeeded to the first inoculation we shall find it to differ in different individuals and we shall also find that it is influenced* by the previous treatment of the *primary symptoms* Where these have been treated on the nonmercurial plan we generally observe that the secondary symptoms are late in appearing and that they are also preceded by less previous disturbance of the system but when mercury has been used for a short time only or has been discontinued as soon as the chancre had healed we shall find in such cases that the secondary symptoms will appear more early (p 120)

Contemporary treatment aside from mercury consisted of sarsaparilla acids alkalies sea bathing and sea air Colles rated all these as of dubious value and was a strong advocate of mercury He stressed the importance of full doses by inunction usually until salivation or diarrhea was attained and also emphasized the need of rest and general upbuilding during or before the treatment in depleted patients There is no indication however that he recognized the need for further therapy after clinical symptoms had disappeared

Turning now to the question of infection in mother and child it may be recalled that "Colles law" as usually formulated states that a non syphilitic mother may nurse her obviously syphilitic child without acquiring any lesion It has been implied that Colles believed the father to be syphilitic under these circumstances and that he had infected the child whereas the mother was not syphilitic at all but had acquired some mysterious sort of protection against infection from her diseased offspring There is not the slightest suggestion however from Colles actual statement that he had any such idea at all *indeed* most of the mothers in the cases actually cited were known to have had syphilis if they were not actually under treatment at the time *Colles simply* wonders why the mother despite the fact that she is syphilitic gets no chancre of the nipple whereas the non syphilitic wet nurse does "It is a curious fact that I have never witnessed nor ever heard of an instance in which a child deriving the infection of syphilis from its parents has caused an ulceration in the breast of its mother (p 285) And later One fact well deserving our attention is this that a child born of a mother who is without any obvious venereal symptoms will infect the most healthy nurse whether she suckle it or *merely* handle it or dress it and yet this child is never known to infect its own mother even though she suckle it while it has venereal ulcers of the lips and tongue" (p 304)

Finally one should mention Colles important observations on non venereal transmission of syphilis "Those who are acquainted with the very scanty furniture of an Irish cabin will readily comprehend with what facility and rapidity the disease can be propagated in this manner but to others it may be necessary to say that the family are quite satisfied with the possession of one single spoon and the stock of cups and cans is nearly as scanty Exposed thus to the double risk of contracting this infection when sleeping or taking nourishment we cannot be surprised at finding three or four in a family of six children all at the same time infected"

12 RICORD Ph Traité pratique des maladies vénériennes ou recherches critiques et expérimentales sur l inoculation appliquée à l étude de ces maladies Paris De Just Rouvier & E Le Bouvier 1838

Ricord criticizes the "error ignorance or bad faith of most of those who have reported the innumerable observations on inoculation of syphilis which have been made since the time of Hunter" (1) to prove the existence of a specific cause of syphilitic diseases the venereal virus (2) to distinguish, among them diseases apparently similar (3) to establish the differences which exist between primary infection and general intoxication (4) with reference to therapy either to prove the efficacy of prophylactic agents or to modify by a new infection a first old and stubborn syphilitic infection or by adding the syphilis to a disease in itself incurable to cause it to yield to special treatment (5) and finally to consider syphilis from the hygienic and medicolegal standpoints (p 2)

The first part of the book (pp 5–198) is devoted to a systematic critique of the contemporary literature on these subjects Many writers denied the inoculability of chancre and following Hunter regarded syphilis and gonorrhea as the results of the same virus Ricord s own ideas are summarized as follows (p 40) "The Chancre during its period of ulceration is always re inoculable [in the same individual] the bubo of absorption is always re inoculable the pustule of inoculation can be reproduced indefinitely by its pus the pus of non ulcerative urethritis is non inoculable" Ricord was obviously dealing mostly with non syphilitic venereal lesions The differentiation of gonorrhea and venereal ulcers was however Ricord s chief contribution and it was documented by numerous detailed clinical experiments in the second part of the book (pp 199–531) He also clearly recognized primary secondary and tertiary stages (p 644) Ricord attempted animal inoculation dogs rabbits guinea pigs cats and pigeons were used unsuccessfully and he concluded that the disease was specific for man He recognized extra genital chancres and believed that the disease was not necessarily venereal

The third portion of the book deals with therapy Ricord evidently had a strong feeling for public health matters and he devotes a section to prevention He urges the thorough examination of prostitutes every three days not superficially but with the speculum Hygienic and cleansing methods are indorsed for both men and women

As to actual therapy Ricord first states that the primary syphilitic ulcer can often heal without any treatment" (p 547) but nonetheless he insists that "the chancre in its beginning imperiously demands abortive therapy I submit in support of this precept that there is no authentic observation of ulcers which destroyed within the first five days after infection have been followed by

secondary symptoms (p 548) He discusses excision and cauterization (p 549) Ricord was evidently confused about the whole question of mercury People apparently got well without it and never again had recognizable trouble others developed secondary syphilis in spite of early use of mercury Many symptoms in syphilitics were at the time blamed on mercury The result of all this led to a rather conservative recommendation and "antiphlogistic" treatment was advised along with mercury as the initial step for secondary manifestations (p 616) Mercury should be given in the confirmed type of syphilis" Mercury is certainly not a specific but it is the most certain and most powerful remedy (p 623) He believed that salivation emphasized as important by many writers was not useful since it interrupted the course of treatment (p 627) Details of methods of using mercury are given (p 623) Tertiary manifestations occur a long time after the primary infection and may be hard to recognize (p 643) They include deep "tubercles" of the skin and mucous membranes "osteocopic" pains periostitis and gummatous tumors In summary Ricord was a keen and honest observer but he was overwhelmed by the complexity of the lesions he dealt with His great contribution was the insistence that syphilis and gonorrhea were different diseases although he was not really the first to make this claim (Refs 2 4)

He went a step further than most others in differentiating secondary and tertiary lesions However he had a very confused idea of the mechanism of secondary lesions He thought the virus of syphilis went to local glands through the lymphatics and thence to the body generally through the blood producing skin lesions but he insisted that no secondary lesion was contagious or inoculable (pp 162 ff 477 ff) He believed that tertiary lesions were also not contagious (p 644) In fact he thought that the farther the virus was from the primary lesion the more it was modified and lost its specificity (p 645) Finally Ricord thought that the primary lesion began as a pustule without incubation period

13 CAZENAVE P L Alphée Traité des syphilides ou maladies vénériennes de la peau Paris Labé 1843

The writer clearly defines the incubation period "In summary the time which elapses without any morbid local or general manifestation from the moment of the infecting contact until the results of infection appear this time I say is a true incubation period during which general poisoning takes place and which is followed inevitably by the specific phenomena of syphilis" (p 147)

14 ROMBERG Moritz Heinrich Lehrbuch der Nervenkrankheiten des Menschen Berlin A Drucker 1846 (English translation of the 2d ed by Edwin H Sieveking M D [2 vols London New Sydenham Society 1853])

Chapter 49 contains Romberg's classical description of tabes in which he emphasizes diminution of muscle sense numbness of feet swaying on standing with eyes closed (Romberg's sign) insecurity of gait especially in the dark urinary difficulty girdle sensation lightning pains in legs etc There is a fairly good gross anatomical description of the cord lesion Romberg emphasizes the slow inexorable course

D Argyll Robertson ("On an interesting series of eye symptoms in a case of

spinal disease with remarks on the action of belladonna on the iris etc Edin burgh M J 14:696 1869) described a frank case of tabes (without naming it as such) in which he noted "I found both pupils contracted to little more than pin points I could not observe any contraction of either pupil under the in fluence of light but on accommodating the eyes for a near object both pupils contracted" There follows a scholarly discussion of the pathological physiology of the condition Argyll Robertson pursued the subject further in another paper (Four cases of spinal myosis with remarks on the action of light on the pupil" *ibid* 15 487 1869)

At about the same time J M Charcot ("Sur quelques arthropathies qui paraissent dépendre d une lésion du cerveau ou de la moelle épinière Arch de physiol norm et path 1:161 1869 2 129 1869) gave a beautiful description of tabetic arthropathy in a number of people with frank locomotor ataxia Inter estingly enough he stated that syphilis among other things had nothing to do with this trouble

W Erb ("Ueber Sehnenreflexe bei Gesunden und bei Ruckenmarkskranken" Arch f Psychiat 5 792 1875) and C Westphal (Ueber einige Bewegungs Erscheinungen an gelahmten Gliedern" Arch f Psychiat 5 803 1875) simul taneously described the knee jerk and its aberrations in disease Westphal (p 819) stated "The knee jerk is constantly absent in patients with the frank clinical picture of tabes dorsalis" (Westphal s sign)

A good review of the history and general features of tabes is to be found in "Syphilis of the Nervous System" in D Arcy Power and J Keogh Murphy *A System of Syphilis* (London Henry Frowde 1910) 4 319 chap x

15 RICORD Philippe Traité complet des maladies vénériennes clinique iconographique d l'hôpital des vénériens Paris J Rouvier 1851

This beautiful atlas with numerous large color plates of venereal lesions is justly famous We do not find a single picture however which seems typical of an uncomplicated primary syphilitic chancre Since many lesions are described as appearing a very few days after contact one wonders whether most of them were not "soft non syphilitic ulcers which seemed extremely prevalent at the time

16 DIDAY P Traité de la syphilis des nouveau nes et des enfants à la mamelle Paris V Masson 1854

This thoughtful well reasoned book is a landmark in the history of congenital syphilis Every conceivable question is taken up and discussed if not answered There are excellent descriptions of the clinical features and comprehensive dis cussions of prognosis and therapy Diday inclines to the view that the mother of a syphilitic child is herself usually but not always syphilitic and that early treatment, first of the syphilitic mother and then of the child itself with mer cury and iodides is in order An apparently healthy child born of syphilitic parents should be treated

17 BASSEREAU P I A Léon Traite des affections de la peau sympto matiques de la syphilis Paris J B Bailliere 1852

This is one of the first books devoted to a careful analysis of syphilitic skin le sions but Bassereau was also noteworthy for discovering by the method of

secondary symptoms" (p 548) He discusses excision and cauterization (p 549) Ricord was evidently confused about the whole question of mercury People apparently got well without it and never again had recognizable trouble others developed secondary syphilis in spite of early use of mercury Many symptoms in syphilitics were at the time blamed on mercury The result of all this led to a rather conservative recommendation and antiphlogistic treat ment was advised along with mercury as the initial step for secondary mani festations (p 616) Mercury should be given in the confirmed type of syphilis "Mercury is certainly not a specific but it is the most certain and most power ful remedy (p 623) He believed that salivation emphasized as important by many writers was not useful since it interrupted the course of treatment (p 627) Details of methods of using mercury are given (p 623) Tertiary mani festations occur a long time after the primary infection and may be hard to recognize (p 643) They include deep "tubercles of the skin and mucous mem branes osteocopic pains periostitis and gummatous tumors In summary Ricord was a keen and honest observer but he was overwhelmed by the com plexity of the lesions he dealt with His great contribution was the insistence that syphilis and gonorrhea were different diseases although he was not really the first to make this claim (Refs 2 4)

He went a step further than most others in differentiating secondary and tertiary lesions However he had a very confused idea of the mechanism of secondary lesions He thought the virus of syphilis went to local glands through the lymphatics and thence to the body generally through the blood producing skin lesions but he insisted that no secondary lesion was contagious or inocula ble (pp 162 ff 477 ff) He believed that tertiary lesions were also not con tagious (p 644) In fact he thought that the farther the virus was from the primary lesion the more it was modified and lost its specificity (p 645) Finally Ricord thought that the primary lesion began as a pustule without in cubation period

13 CAZENAVE P L Alphée Traité des syphilides ou maladies vénériennes de la peau Paris Labé 1843

The writer clearly defines the incubation period In summary the time which elapses without any morbid local or general manifestation from the moment of the infecting contact until the results of infection appear this time I say is a true incubation period during which general poisoning takes place and which is followed inevitably by the specific phenomena of syphilis" (p 147)

14 ROMBERG Moritz Heinrich Lehrbuch der Nervenkrankheiten des Menschen Berlin A Drucker 1846 (English translation of the 2d ed by Edwin H Sieveking M D [2 vols London New Sydenham Society 1853])

Chapter 49 contains Romberg s classical description of tabes in which he em phasizes diminution of muscle sense numbness of feet swaying on standing with eyes closed (Romberg s sign) insecurity of gait especially in the dark urinary difficulty girdle sensation lightning pains in legs etc There is a fairly good gross anatomical description of the cord lesion Romberg emphasizes the slow inexorable course

D Argyll Robertson ("On an interesting series of eye symptoms in a case of

20 VIRCHOW R Ueber die Natur der constitutionell syphilitischen Affectionen Berlin G Reimer 1859 also in Virchows Arch f path Anat 15 217 1858

This book must be mentioned in the bibliography because of the universal recognition it met with for years and because of its author s great name Actually one finds little of exceptional value in it The remarks are based on gross morbid examinations and it is questionable whether all the lesions were syphilitic Under the heading of "Syphilis of the Heart" for example one finds a description of a lesion designated as aneurysm (not of the aorta but of the heart) which is clearly due to infarction of the muscle and not to syphilis The book is however a milestone in the study of syphilis from the standpoint of emphasizing how widespread the lesions may be

21 GROS Léon Des affections nerveuses syphilitiques Paris A Delahaye 1861

This book of nearly five hundred pages deals comprehensively with syphilis of the central nervous system The conclusions which are formulated at the end of the book in 89 statements are based on reports of 269 cases from the literature which are given in abstract Many of these were undoubtedly syphilitic but probably not all the writer based the diagnosis on history and other manifestations of syphilis and the response to specific therapy The cases are divided into "affections without appreciable lesion," "convulsive neuroses" "paralytic neuroses" "asthma" and troubles of intelligence" Some of the latter patients may have been paretics

Some of the conclusions are (I) nervous affections can develop at any period of constitutional syphilis (II) these affections may involve sensibility motility or intelligence (III) they may stimulate all sorts of other (non syphilitic) affections

It is obvious that with the means at hand correct diagnosis could not be made in every case but the problem of central nervous system syphilis is clearly defined

22 ROLLET J Recherches cliniques et expérimentales sur la syphilis le chancre simple et la blennorrhagie Paris J B Baillière et fils 1861

Rollet s book is much more modern in tone than any of the preceding monographs He regards the following points as established Gonorrhea is a specific disease (p 8) Simple ulcer of the genitals is repeatedly reinoculable in the same individual it is not syphilitic (p 10) Syphilitic chancre is never reinoculable in the patient who has it although it is transmissible to others (p 14) Syphilitic chancre cannot be inoculated in anyone who has syphilis no matter in what stage (p 12) Several chancres may develop at the same time but never successively (p 12) True syphilitic chancre may occur in the mouth on the nipple or elsewhere (pp 13 242 248) Of the three "venereal" diseases—gonorrhea chancroid and syphilis—the last because of its multiple situation and its variable mode of transmission is certainly the least venereal of the three (p 14) The incubation period of syphilis varies from 9 to 42 days average 25 (p 15) The syphilitic chancre rests on a hard base which feels like a lump of rubber or cartilage (p 16) Secondary syphilis always follows a true syphilitic chancre never any other venereal disease (p 18) The incubation period of

confrontation the duality of soft and hard (syphilitic) ulcers If one confronts all the subjects who have had chancre followed by constitutional syphilis with the subjects who communicated the contagion to them or with those to whom they have transmitted it one finds that all these subjects without exception have had chancres followed by constitutional accidents Never among them has the chancre limited itself to a purely local action If on the contrary one confronts the subjects who have chancres which have not led to any symptoms of general syphilis with the people who have infected them or whom they have infected one finds that these without exception have chancres which have limited their action to the point of first contamination (p 197)

18 CLERC F F Considérations nouvelles sur le chancre infectant et le chancroid Union med 9 509 1855

Clerc found that if one inoculated people with tertiary or with primary syphilis with material from a syphilitic chancre one would fail to produce a lesion in the vast majority of cases whereas if one used material from chancroidal ulcer one could succeed in practically every case Thus he definitely differentiated the two diseases

19 FOURNIER Alfred Leçons sur le chancre professées par le Docteur Ricord Paris A Delahaye 1858

The writers were struck by the differences between the effects of various primary sores—some were followed by constitutional manifestations whereas others never were This suggested that these were different diseases of different causation They distinguished soft chancre (chancroid) and syphilitic chancre "The inoculability of the pus secreted is the sign absolute of the non syphilitic sore The indurated slow ulcer on the other hand, is syphilitic and is followed by constitutional phenomena—secondary and tertiary They did not however regard the secondary lesions as contagious although they could be transmitted by heredity (p 134) Their great conclusion was that the two diseases were the results of entirely different viruses There is an immense amount of detailed discussion and numerous case reports which do not always clarify the issue because of difficulty in making a definite differential diagnosis of hard and soft chancres and because of uncertainty about the significance of later lesions

As to therapy the writers believed that all chancres were at first a *local* disease before a constitutional spread took place In this early stage they advised (during the first four days) cauterization This doctrine was based on the fact that they had never seen constitutional symptoms following chancre (see Ref 11) destroyed before the fifth day (p 207) If the chancre was seen later then the treatment was that of the constitutional diathesis—mercury An indurated primary lesion always called for mercurial therapy They did not favor pushing mercury to the point of salivation—"The curative action of mercury is generally suspended when the marked symptoms appertaining to this drug are produced" (p 214) Six months of mercury followed by three of iodide such is the medication gentlemen which gives the most sustained cures in the enormous majority of cases" (p 221) The book concludes (p 223) with a precise summary of the difference between soft and hard chancres including emphasis on reinoculability of soft chancre and absence of inoculability of hard syphilitic sores

In this intensive description of the histology of arteries by the use of modern histological methods we find what we believe may be an account of syphilitic aortitis although the author does not associate the process with syphilis (p 220)

26 LANCEREUX E Traité historique et pratique de la syphilis Paris J B Baillière et fils 1866

This volume of some eight hundred pages is a landmark in the literature of the subject It is especially noteworthy because of the detailed references to the literature Lancereux clearly distinguished the stages of syphilis There is an elaborate discussion of the incubation period which he regarded as the first stage of the disease He found it to be 24 days more or less The period of "local eruption" is the time from the first appearance of the chancre until the first general manifestations The various clinical types of chancre and associated adenopathy are described in detail The secondary lesions appear 40-50 days after the appearance of the chancre and they affect especially the superficial layers of skin and mucous membranes and usually leave no scars They "consist of a chronic hyperemia accompanied sometimes by a serous or purulent exudate but never by the production of the connective tissue masses called gummata" (p 117) There are however "superficial" invasions of organs such as muscles bones eyes and joints with headaches and fever These lesions are all discussed in minute detail as are those of the tertiary stage the feature of which is gummata destructive in contrast to secondaries In the several hundred pages on gummata one looks with interest at the sections on cardiovascular and central nervous system syphilis Gummatous myocarditis is described but nothing which can be reconciled with syphilitic aortitis So too with the nervous system there is no mention of tabes or paresis although there are described many inflammatory lesions the exact nature of which is not clear

There is an interesting discussion on the outcome of syphilis and the question of whether it is ever cured (p 525) There is a long section on congenital syphilis and a clear distinction is drawn between "hâtive and "tardive" types

As to the actual cause of syphilis Lancereux felt that it was something in the clear secretion of the chancre that pus was less contagious The virus in the secondary stage was in the blood and was then communicable Contagion might be any sort of contact not necessarily venereal As to therapy mercury was in use by medieval Arabian physicians as a treatment for skin disease and was used for syphilis first about 1497 The work on iodides is reviewed (p 700) Other components of antisyphilitic therapy are discussed

It is seen then that syphilis had come a long way from Hunter It was now definitely recognized as a specific contagious disease The various stages and incubation periods were clearly defined The lesions were classified although treatment did not progress further for fifty years It was recognized that primary and secondary lesions would communicate the disease to others but were not reinoculable on the same person Central nervous system syphilis was diagnosed and there were the beginnings of realization that tabes dorsalis was syphilitic

27 PARROT J Sur une pseudo-paralysie causée par une alteration du systeme osseux chez les nouveau nés atteints de syphilis héréditaire Arch de physiol norm et path 4 319 1872

secondary syphilis varied from 12 to 128 days average 52 days after the first appearance of the chancre (p 18) Cauterization of a syphilitic chancre does not prevent secondary lesions (p 23) Various venereal diseases may coexist accidentally (p 31) The virus of syphilis is not only in the chancre but spreads through the blood to every tissue in the body the contagious principle of gonorrhea and chancroid is confined to the local lesion (p 46) Secondary syphilis is definitely contagious (p 237) as everyone before Hunter believed. Secondary syphilis transmitted to another person produces a *primary chancre* (p 310)

There is a comprehensive chapter on methods of contagion between nurses and infants and a discussion of medicolegal questions

Rollet believed that chancre could be produced by inoculation of syphilitic blood (p 344) and that syphilis could be transmitted by smallpox vaccination (p 351) As to treatment he thought that cauterization of a chancre even when it first appeared, would not prevent secondaries (p 516) The chapter on mercurial therapy is of special interest Rollet attributed the use of mercury to Arabic physicians of the sixteenth century He analyzed the literature on the non mercurial treatment of syphilis (p 567) a method which spread like an epidemic all over Europe between 1817 and 1840 Rollet also discussed syphili zation " a term which was currently in vogue (p 576) He credited Wallace (Ref 9) with introducing potassium iodide as a therapeutic agent (p 580) As to the actual use of mercury and iodides Rollet individualized Some cases were easy to cure some difficult (p 584) He did not believe in pushing the drugs until severe symptoms (salivation) appeared He thought it important to sup port the general condition with cod liver oil and other measures

The book is especially valuable for its historical summaries

23 HUTCHINSON Jonathan Clinical lecture on heredito syphilitic struma and on the teeth as a means of diagnosis Brit M J 1 515 1861

In connection with a child aged eleven with an ulcer on the tibia Hutchinson makes the diagnosis of congenital syphilis on the basis of the teeth "Remember that it is the permanent set only which show any peculiarities "The central upper incisors are the test teeth You may neglect all the others The teeth are short and narrow Instead of becoming wider as they descend from the gum they are narrower at their free edges than at their crowns their angles having been as it were rounded off In the center of their free edges is a deep vertical notch "

24 WILKS Samuel On the syphilitic affections of internal organs *Guys* Hosp Rep 9 3d ser 1 1863

This much quoted paper is mainly of negative value since many of the cases—of disease of the liver for example—are doubtful and since lesions of the aorta are not mentioned except the case of a prostitute with abdominal aneurysm " There was no concept at the time however of syphilitic arteritis in the modern sense

25 LANGHANS Th Beitrage zur normalen und pathologische Anatomie der Arterien Virchows Arch f path Anat 36 187 1866

nized. Gowers later (Syphilis and locomotor ataxy " Lancet 1 94 1881) wrote again on the subject with even greater confidence He was inclined to think that the cases following obvious syphilis and those in which there was no history were nonetheless all the same—probably syphilitic. No case of tabes was met with earlier than seven years after the syphilitic infection Erb (Ueber die aetiologische Bedeutung der Syphilis fur die Tabes dorsalis " Tr Internat Med Congr London 2 32 1881) summarized the whole subject once more at the International Medical Congress It is interesting that the eight eminent men who discussed Erb s paper almost without exception were skeptical as to the close relation of syphilis to tabes

Finally Fournier in a book of nearly four hundred pages (*De l'ataxie loco motrice d'origine syphilitique* [Paris C Masson 1882]) analyzed every aspect of the subject and concluded "Major conclusion Treat early syphilis long and energetically to prevent the serious manifestations of a later stage to prevent especially one of its most redoubtable manifestations tabes" (p 396)

As late as 1910 however tabes and general paresis are spoken of as "para syphilis"—"the term given by Fournier to those diseases of which syphilis is essentially the cause but which are not directly the result of the syphilitic virus" (see F W Mott "Syphilis of the nervous system " in D Arcy Power and J Keogh Murphy *A System of Syphilis* [London Henry Frowde 1910] 4:186)

30 WELCH Francis H On aortic aneurism in the army and conditions associated with it M Chir Tr 41 59 1876

In a comprehensive article Lewis A Connor ("Development of knowledge con cerning role of syphilis in cardio-vascular disease J.A.M.A. 102 575 1934) reviews the early work on the relation of syphilis to cardiovascular disease There are a few hints as to a relation of aneurysm to syphilis but credit for de scribing a specific aortic lesion associated with aneurysm and for insisting on the syphilitic nature of the process clearly goes to Welch Working with autopsy material from the army he described two forms of aortic disease one a general form with which people do not die and the second a specific form associated with aneurysm leading to early death

"The deduction arrived at may be placed in the form of two propositions 1 That the aneurismal tumors are associated with and preceded by a diseased condition of the contiguous layers of the intimal and middle coats of the ves sel—a tissue growth terminating in degeneration—which by impairing the elasticity and contractility of the walls allows of their expansion and dilatation under the tension of normal arterial blood pressure 2 that the struc tural growth is in the major number of instances associated with syphilis and in a minor degree with rheumatism and alcoholism as causations hence it follows that the means for the prevention of the aneurismal tumour must be essen tially directed toward elimination of the special exciting agencies "

31 FOURNIER A De la pseudo-paralysie général d origine syphilitique Progr méd Paris 5 761 1877

It is impossible to assign to any one man the definite recognition of paresis and tabes as syphilitic In this lecture by Fournier he points out that many have raised the question without proof His own point is that "true general paresis" is not syphilitic but that a distinguishable although similar "pseudo general

"This work is a contribution to the pathology of the newborn and very young infants We propose to make known a state which simulates paralysis and of which the cause is a lesion of bone due to congenital syphilis This important condition is described at length and there is a beautiful colored plate The original article is reprinted in Parrot s book (*La Syphilis héréditaire et la rachitis* [Paris G Masson 1886]) together with various other articles on congenital syphilis

28 HUEBNER O Die luetische Erkrankung der Hirnarterien Leipzig F C W Vogel 1874

Of the various monographs of the time on the subject of cerebrovascular syphilis this one is outstanding It begins with a comprehensive historical summary and then gives abstracts of all the reported fatal cases with autopsy including three of the author s own Next comes a section on the anatomy of syphilitic arterial disease One looks in vain for a description in the case of the aorta, of anything resembling syphilitic mesoartitis the lesions are described as mainly in the intima Associated gummata are also described and the lesions are differentiated from ordinary atheroma The physiology of occlusion of syphilitic arteries is then gone into and finally the symptomatology the striking features of which are headache followed by a hemiplegia or other cerebral accident The occurrence at an early age is emphasized Under therapy mercurial inunctions and large doses of potash are advised This is a comprehensive summary of the subject from which any remarks about tabes or paresis are conspicuously absent

29 FOURNIER Alfred De l ataxie locomotrice d origine syphilitique Ann de dermat et syph 7 187 1875–76

On the basis of past history of syphilis in patients with locomotor ataxia Fournier felt sure that syphilis was a cause of the disease in certain cases He did not however look on tabes as an absolutely specific disease and he was not clear whether syphilis acted as a "predisposing factor or whether the lesion was actually syphilitic

Fournier was not however the first to notice the association of syphilis with tabes As long ago as 1859 [G] Duchenne ("De l ataxie locomotrice progressive Arch gén de méd 1 [5th ser Vol 13], 417 1859) said "Several subjects have undergone a constitutional syphilitic infection and he clearly raised the question of whether syphilis was not the cause of tabes

Actually the relation of syphilis to tabes was being discussed on all sides at about this time on the basis of the frequency of a positive history Thus E Vulpian (*Maladies du systeme nerveux maladies de la moelle* [Paris O Doin 1879] p 245) states There are really few patients with locomotor ataxia who have not had several years before the first symptoms of this affection an infecting chancre and secondary syphilitic accidents " W Gowers ("Syphilitic neurosis Brit M J 1 303 1879) felt the same and pointed out, as had others the futility of conventional antisyphilitic therapy W Erb ("Zur Pathologie der Tabes dorsalis " Deutsches Arch f klin Med 24 1 1879) has a comprehensive article with review of both sides of the literature and a thorough discussion of the relation of syphilis to tabes He was puzzled by the fact that "syphilitic and "non syphilitic instances of tabes could not be differentiated and he did not grasp the point that in the latter group the syphilitic infection was unrecog

(III) cranial and nasal deformities (IV) bony deformities of the trunk and limbs (V) cicatricial stigmata of the skin and mucous membranes (VI) ocular lesions (VII) lesions and troubles of the auditory organ (VIII) dental malformations (IX) testicular lesions Whether all the lesions here described are really syphilitic or not one cannot say but Fournier delineated and defined the subject

36 BALZER M F Expériences sur la toxicité du bismuth Compt rend Soc de biol 1:9th ser 537, 1889

Balzer as a preliminary to its use in syphilis reported toxicity studies with subcutaneous injections of various bismuth preparations (citrate of bismuth and ammonia) in dogs He believed that it would be necessary to follow the excretion of bismuth in the urine and warned against sudden signs of intoxication especially stomatitis

Bismuth was not actually used in the treatment of syphilis until 1921 (R. Sazerac and C Levaditi "Traitement de la syphilis par le bismuth" Compt rend Acad d sc 173 338 1921)

37 ERB W I Ueber syphilitische Spinal Paralyse Neurol Centralbl 11 161 1892

In this article Erb describes the syphilitic spastic spinal paralysis which bears his name today A perusal of the article however leaves one unconvinced as to the exact nature of the disorder He points out as differential features from "spastic spinal paralysis" that there are very active tendon reflexes but relatively little spasticity that the bladder is often affected and that there is some disturbance of sensibility This all seems vague however and his main point is the history of syphilis in every case A study of Erb s former article on spastic paralysis ("Ueber die spastische Spinal Paralyse" Virchows Arch f path Anat 70 241 293 1877) shows no convincing difference between the cases described there and those in the later paper although in connection with the first he states definitely that syphilis played no part Just what Erb was really dealing with it is now impossible to say especially as many cases of the "syphilitic" syndrome do not have positive serology and no spirochetes are found at autopsy

38 JARISCH Adolph Therapeutische Versuche bei Syphilis Wien med Wchnschr 45 722 1895

"The present findings are based on an observation which has surely been made by many syphilologists but which to my knowledge has heretofore not been appraised I mean the observation of a reaction whereby in the first days of mercurial inunctions for syphilitic roseola there is an exaggeration of the clinical manifestations" He thought that this reaction was connected with the more rapid involution of the lesions Jarisch goes on to speculate about the mechanism of the reaction and to report some cases K Herxheimer and Krause a few years later ("Ueber eine bei syphilitischen vorkommende Quecksilberreaction" Deutsche med Wchnschr 28 895 1902) describe the phenomenon more in detail They point out the conversion of a syphilitic roseola to an erythema multiforme like eruption with rapid clearing and also describe constitutional reactions—fever glandular enlargement and headache They emphasize the diagnostic value of the reaction and speculate about its nature

paresis *is* syphilitic The evidence rests largely on one case which is reported in detail Fournier thought that he could make definite clinical and anatomical distinctions He gave his method of treating central nervous system syphilis with alternating courses of mercury and iodide in another article ("Traitement de la syphilis du cerveau [leçon clinique]" Bull gén de thérap 96 1 1879) *and he reviewed still elsewhere (La Syphilis du cerveau [Paris G Masson* 1879] p 333) the whole question of paresis and syphilis There is also a large casuistic literature made up of individual case reports which are very hard to interpret as for example that of F Esmarch and W Jessen "Syphilis und Geistesstorung" Allg Ztschr f Psychiat 14 20 1857

32 BERGER Oscar and ROSENBACH Ottomar Ueber die Coincidenz von Tabes dorsalis und Insufficienz der Aortenkleppen Ber klin Wchnschr **16** 402 1879

In a brief communication the authors point out the association of tabes dorsalis and aortic insufficiency nothing is said about syphilis They never observed any other valve lesions with tabes and the patients were in the late thirties to fifties So too Babinski (Des troubles pupillaires dans les aneurismes de l aorte" Bull et mém Soc Méd d hôp de Paris **18** 1121 1901) reports two women with aneurysm aortic insufficiency irregular fixed pupils and diminution of knee jerks In the discussion Marie stated "We know that aortic lesions are common in tabetics"

33 CORNIL V Leçons sur la syphilis Paris J B Bailliere et fils 1879

Although this is a general treatise on syphilis the original part of the work as the author says in the Preface is the histological study of the lesions Beginning with chancre, he goes through every sort of syphilitic lesion with gross and microscopic descriptions and with a series of plates One looks in vain for any *description of aortic syphilis or tabes*

34 FOURNIER Alfred Syphilis et mariage Paris G Masson 1880

Social consciousness in regard to the dangers of syphilis developed early among European physicians (Ref 12) but it remained for the great French syphilographer Fournier to embody all the doctrines about syphilis and marriage in this book of nearly three hundred pages *He* saw clearly that the longer the time which had elapsed since infection (3–4 years as a minimum) and the more thorough treatment given the safer it was for a person to marry The disasters which could ensue for the patient partner and children are so clearly brought out that for the next generation they were common knowledge and the dire results of syphilis and marriage were a not uncommon topic in the lay literature *(cf A Conan Doyle 'The third generation in Round the Red Lamp* [London Methuen & Co *1894])*

35 FOURNIER Alfred. La Syphilis héréditaire tardive Paris G Masson 1886

In this monumental book Fournier sets the stage for all time with reference to late hereditary syphilis that is syphilis occurring at least 3 years—often much later—after birth Fournier groups the findings as follows (I) constitution habitus facies (II) retardation imperfections arrest of physical development

Neumann points out that as yet no causal organism had been identified and that it had not been possible to transmit the disease to an animal Primary secondary and tertiary stages are described and a fourth stage consisting of cachexia amyloid marasmus phthisis pulmonalis etc but not of aneurysm or tabes Many of the lesions described are obviously not syphilitic such as "syphilis of the stomach" "syphilitic" arteritis "gummata" of lung etc

The question of syphilis of blood vessels is reviewed and the relation to aneurysm is described but no specific syphilitic mesaortitis is recognized Aneurysm of the ascending and thoracic aorta is regarded as syphilitic in about 50 per cent of the cases with rheumatism alcoholism and other things as causes of the rest. A tabetic form of syphilis is recognized but just as Fournier thought twenty five years previously syphilitic tabes is just one form of a non specific disease

41 FOURNIER Alfred Prophylaxie de la syphilis Paris J Rueff 1903

By this time the Academy of Medicine justly aroused by the "terrible morbidity" of syphilis appointed a commission to study the question of prevention This volume of over five hundred pages is the result Modes of contagion and of prevention are gone into in the greatest detail and there are chapters on instructing the youth on the venereal peril control of prostitution etc

42 METCHNIKOFF É. and ROUX É Etudes expérimentales sur la syphilis Ann Inst. Pasteur 17 809 1903

The authors review the meager literature on claims of transmission of syphilis to animals The elaborate article of E Klebs (Arch f exper Path u Pharmakol **10** 161 1879) is referred to although a reading of it leaves one unconvinced that Klebs transmitted anything One must remember that before the discovery of the spirochete one had only clinical appearances to go by Metchnikoff and Roux describe the case of one monkey in which they produced by inoculation of material from a human chancre a lesion of the vulva which was pronounced a chancre by Fournier and other experts It seems to us probable that the writers did transmit syphilis to this animal. They conclude among other things that infection causes a prompt immunity since a second inoculation 5 days after the first failed to produce a lesion Others soon got to work on the same problem including A Neisser ("Meine Versuche zur Uebertragung der Syphilis auf Affen" Deutsche med Wchnschr **3** 1309 1904) who was able to produce lesions in chimpanzees Neisser and others at this time when serum therapy was so much in vogue hoped to obtain a therapeutic serum—a hope which of course failed Neisser (*Die experimentelle Syphilisforschung* [Berlin Julius Springer 1906]) gives an authoritative review of the whole subject The early work was soon amplified after the discovery of the spirochete (Ref 44) and the serodiagnostic tests so that immense activity took place among investigators of experimental syphilis

43 RAVAUT Paul Étude cytologique du liquide céphalo rachidien chez les syphilitiques Ann de dermat et syph 4 4th ser 1 1903

At the meeting of February 14 1902 of the Medical Society of the Hospitals of Paris F Widal ("Cytologie du liquide céphalo rachidien des syphilitiques" Bull et mém Soc méd d hôp de Paris **19** 3d ser 118 1902) stated that

39 DOHLE Ueber Aortenerkrankung bei Syphilitischen und deren Beziehung zur Aneurismenbildung Deutsches Arch f klin Med 55 190 1895

The clear definition of a specific syphilitic lesion of the aorta as a prerequisite of aneurysm clearly belongs to Dohle His paper begins with a statement that the occurrence of aortic disease in syphilitics is a well known fact but that the lesions found at autopsy have not been regarded as specifically syphilitic He quotes the case first described by himself ("Ein Fall von eigentumlicher Aortenerkrankung bei einem Syphilitischen" Inaug disst Kiel 1885) and now adds two more There are several illustrations showing well the corrugated barklike appearance of the ascending aorta The histology is described in detail and the following conclusions are drawn "(1) Syphilitic inflammation of the aorta is macroscopically recognized by starlike scarred puckerings of the inner surface In addition, there may be a thickening of the intima (chronic endarteritis) The depressions are caused by diffuse and gummatous inflammation in the media and the adventitia which lead to formation of scarred connective tissue (2) The inflammatory changes in the media make possible the formation of aneurysms"

The work of Dohle and others from the Pathological Institute at Kiel on the subject was not generally accepted and finally Arnold Heller the chief of the laboratory was stimulated to speak himself on the subject at a meeting of the German Pathological Society ("Ueber die syphilitische Aortitis und ihre Bedeutung fur die Entstehung von Aneurismen" Verhandl d deutsch path Gesellsch Berlin 1 346 1899) in support of his pupils Heller's remarks are followed by a paper on similar changes in the aorta in general paresis (Straub "Ueber die Veranderungen der Aortenwand bei progressiver Paralyse" Verhandl d deutsch path Gesellsch Berlin 1 351 1899)

The remarks of Heller and Straub were followed by a general discussion, in which the speakers were thoroughly disbelieved and castigated by most of the outstanding pathologists of Germany—Ponfick Hansemann Baumgarten Ziegler Orth Chiari and Babes Not a voice was raised in agreement

However by 1903 at the meeting of the same society H Chiari ("Ueber die syphilitischen Aortenerkrankungen" Verhandl d deutsch path Gesellsch Berlin 6:137 1903) in a review of the subject somewhat grudgingly admitted that the Heller school was correct "If we take the results of this material, we come to the conclusion that this form of aortitis can be caused by syphilis C Benda ("Aneurisme und Syphilis" Verhandl d deutsch path Gesellsch Berlin 6 164 1903) in a long "Korreferat" came to the same conclusion, which has never since been in doubt Good summaries of the whole subject are those of Fahr ("Zur Frage der Aortitis syphilitica," Virchows Arch f path Anat. 177 508 1904) and of W T Longcope (Syphilitic aortitis its diagnosis and treatment" Arch Int. Med 2 15 1913)

40 NEUMANN Isidor Syphilis Vienna Alfred Holder, 1899

This large volume from the Nothnagel system gives an authoritative review of knowledge of syphilis at the turn of the century It is of interest how little progress had been made in fifty years That had to wait for the discovery of the spirochete and the Wassermann test

SYPHILIS PART II FROM THE DISCOVERY OF THE TREPONEME (1905)

various observers in his clinic had found a lymphocytosis in the spinal fluid of tabetics paretics and syphilitics with severe headaches It remained for Ravaut, however to study systematically the fluid of syphilitics to confirm and amplify the above observations and to point out that lymphocytosis in patients with no overt clinical findings might indicate an asymptomatic central nervous system syphilis and might be the precursor of an overt outbreak of neurosyphilis

44 SCHAUDINN Fritz and HOFFMANN Erich Vorlaufiger Bericht uber das Vorkommen von Spirochaeten in syphilitischen Krankheitsprodukten und bei Papillomen, Arb a d k Gsndhtsamte Berlin 22 527 1905

A commission was appointed to search for living organisms in syphilitic lesions A happy choice of Schaudinn a highly qualified bacteriologist was made with Hoffmann, a fine clinician and syphilologist to work with him In smears both from the surface and from the depths of primary untreated lesions as well as from glands spirochetes were demonstrated those characteristic of syphilis were very "pale slender and showed many small angulations Schaudinn named them *Spirochaeta pallida* in contrast to other coarser forms found on the genitalia —*S refringens* The organisms were first seen in fresh preparations but stained fairly readily with aniline dyes The spirochetes were *not* found in papillomata

The story of the events leading up to the discovery of the spirochete is vividly told by Metchnikoff (The Microbiology of Syphilis" in D Arcy Power and J Keogh Murphy, *A System of Syphilis* [London Henry Frowde 1908] I 43)

S refringens By this time they had demonstrated *pallida* not only in primary lesions but in the spleen (puncture autopsy) and liver of a child dead of con genital lues All these findings were soon confirmed by B Kiolemenoglou and Felix v Cube (Spirochaete pallida [Schaudinn] und Syphilis" Munchen med Wchnschr 52:1275 1905) although it is of interest that in the same journal a few weeks later there appeared an article (J Siegel "Neue Untersuchungen uber die Aetiologie der Syphilis" p 1321) in which a flagellate was found in primary lesions and lymph nodes and was put forward as the cause—*Cytorryctes luis* Meanwhile as acute an observer as C Fraenkel (Ueber das Vorkommen der Spirochaete pallida bei Syphilis" Munchen med Wchnschr 52 1129 1905) lent his support to Schaudinn and Hoffmann Bille ("Ueber Spirochaeten befunde bei Syphilis" 52:1377 1905) reviews the accumulating literature and adds confirmatory observations of his own as does H Ploeger ("Die Spirochaten bei Syphilis" Munchen med Wchnschr 52 1381 1905) C T Noeg gerath and R Staehelin ("Zum Nachweis der Spirochaete pallida im Blut Syphilitischer" Munchen med Wchnschr 52 1481 1905) claimed to have demonstrated *S pallida* in centrifuged blood of a patient with secondary syphi lis In view of later proof of transfusion syphilis (Ref 28) this may have been correct Ploeger ("Ueber Spirochäten bei Syphilis" Munchen med Wchnschr 52 2394 1905) describes the demonstration of *S pallida* in skin lesions of syph ilis

From this time on there were innumerable reports on the findings of spirochetes in various organs [1] A full bibliography of the earlier literature is found in S Sobernheim "Syphilisspirochate" in W Kolle and A von Wassermann *Handbuch der pathogenen Mikroorganismen* (2d ed. Jena Gustav Fischer 1913) 7 812 whereas more recent work is summarized in a later edition of the same treatise (3d ed. 1930) 7: Part I 31)

A vast amount of work has been done on the morphology and life-cycle of the spirochete (see for example E V De Lamater R H Wiggall, and M Hannes Studies in the life cycle of spirochetes" J Exper Med 92:239 247 1950)

3 BERTARELLI E Ueber die Transmission der Syphilis auf das Kanin chen, Centralbl. f Bakt 41 320 1906

Following the transmission of syphilis to monkeys by Metchnikoff and Roux and the discovery of the parasite innumerable attempts were promptly made to transmit syphilis to all sorts of animals Claims and denials were abundant Bertarelli was the first definitely to transmit syphilis to rabbits a feat of great importance since rabbit infection has been used extensively in studying problems of immunity in syphilis Bertarelli ground up material obtained from the center of a "syphiloma" and rubbed it into the lightly scarified cornea of a rabbit Inoculation was made on January 31 on February 10 a slowly progressive lesion of the cornea appeared On February 13 the eye was removed and showed "myriads" of spirochetes which had the characteristics of *pallida*

[1] Much of this work was done with the dark field technique See E Friedberger and H Reiter "Die allgemeinen Methoden der Bakteriologie" in Kolle and Wassermann *Handbuch der pathogenen Mikroorganismen* (2d ed. Jena Gustav Fischer 1912) 1 305 and Hideyo Noguchi, *Laboratory Diagnosis of Syphilis* (New York Paul B Hoeber 1923) pp 251 ff

SYPHILIS PART II

WITH the great discoveries made in syphilis during the first decade of the century—transmission to animals identification of the spirochete the Wassermann test and Salvarsan—the entire aspect of the disease underwent a change To clinical intuition and experience were added precise methods of study and rational control of therapy The literature pursued several lines to the old clinical studies were added those of experimental syphilis in animals isolation of the spirochete from human lesions serodiagnostic tests, immunity in syphilis and arsenical chemotherapy Finally a new era dawned with the discovery that penicillin was treponemacidal and at long last there seems to be a real prospect of eliminating syphilis as a significant disease We have tried to refer to the important key articles along these various lines For a comprehensive bibliography however reference is made to the annual reviews of syphilis in the Archives of Internal Medicine of which the nineteenth has recently appeared (H Beerman I L Scharnberg L Nicholas and L Katzenstein "Syphilis review of recent literature Arch Int Med 95 256 1955)

1 METCHNIKOFF É and ROUX E Etudes expérimentales sur la syphilis quatrième mémoire Ann Inst Pasteur 19 673 1905

This is the writers fourth and final report on transmission of syphilis to monkeys In 22 chimpanzees inoculated with virus of diverse origin we have not a single failure to report all presented definite syphilitic manifestations The incubation period varied from 15 to 49 days on the average it has been 30 days" Meanwhile Schaudinn had discovered the spirochete and the writers succeeded in demonstrating the parasite in most of their monkeys with experimental syphilis

A comprehensive discussion of monkey syphilis is that of Albert Neisser (*Beitrage zur Pathologie und Therapie der Syphilis* [Berlin Julius Springer 1921])

2 SCHAUDINN Fritz and HOFFMANN Erich Ueber Spirochaetenbefunde im Lymphdrusensaft Syphilitischer Deutsche med Wchnschr 31 711 1905

Schaudinn s first announcement of the discovery of the spirochete (Fritz Schaudinn and Erich Hoffmann "Vorlaufiger Bericht uber das Vorkommen von Spirochaeten in syphilitischen Krankheitsprodukten und bei Papillomen" Arb a d. k. Gsndhtsamte 22:527 1905) was followed by innumerable reports of search for the organism in various syphilitic tissues Schaudinn and Hoffmann again stress the difference between a dark readily stainable and a pale difficultly demonstrable spirochete—the latter presumably the cause of syphilis In this paper they report finding spirochetes in eight instances of enlarged inguinal glands in cases of early syphilis In another paper the same writers ("Ueber Spirochaete pallida bei Syphilis und die Unterschiede dieser Form gegenuber anderen Arten dieser Gattung" Berl klin Wchnschr 42 673 1905) discuss further (with an illustration) the difference between *Spirochaeta pallida* and

the antibody in syphilitics with the conclusion that the reaction was at any rate *clinically* specific Landsteiner also opened the question of false positive tests (Ref 34) by finding that the sera of animals infected with *Trypanosoma gambiense* fixed complement C Levaditi and T Yamanouchi ("Le Séro-diagnostic de la syphilis" Compt rend Soc. de biol 63:740 1907) also found that alcoholic extracts of liver as well as suspensions of sodium taurocholate and glycocholate served as antigens and they concluded that a positive test was not brought about by specific antibodies in the usual sense but that this fact did not lessen the practical value of the procedure Carl H Browning John Cruickshank, and Ivy M'Kenzie ("Constituents concerned in the Wassermann reaction with special reference to lecithin and cholestrin" J Path & Bact 14 484 1909–10) showed that the addition of cholesterol to Wassermann antigens had a fortifying effect which made them more sensitive

From this point on, an immense literature on the Wassermann reaction and on other serodiagnostic tests (flocculation) for syphilis has developed which is summarized in a number of books of which these are important H Noguchi *Serum Diagnosis of Syphilis and the Butyric Acid Test for Syphilis* (Philadelphia and London J B Lippincott Co 1910) R L. Kahn *The Kahn Test A Practical Guide* (Baltimore Williams & Wilkins Co 1928) Harry Eagle *The Laboratory Diagnosis of Syphilis* (St. Louis C V Mosby Co 1937) Josephine Henrichson *Modern Serologic Tests for Syphilis* (Ven Dis Inform Suppl No 14 [1941]) Eagle s book is especially useful because of its full theoretical discussion of the reactions and its bibliography

6 EHRLICH Paul, and HATA S Die experimentelle Chemotherapie der Spirillosen. Berlin Julius Springer 1910

The name of Paul Ehrlich is inextricably bound up with the great modern era of chemotherapy of syphilis In this book Ehrlich tells the story of the development of knowledge—how he had always thought that the key to chemotherapy was the finding of drugs which had a special affinity for chemoreceptors of the parasite rather than for those of the host how he became interested in arsenic compounds the first of which were ineffective or toxic and finally how in animal experiment first with trypanosomes and spirilloses and finally with syphilis dioxydiaminoarsenobenzol—the 606th compound developed and tested—yielded definite beneficial results Ehrlich distributed small amounts of the material to various clinicians and clinics for trial at the end of the book (p 161) is a list of papers which had appeared up to October 1910 on the practical use of the compound At first, it was given in one dose of 0 3 gm intramuscularly Lesions melted away and treponemes were seen to disappear rapidly from chancres Later it was found to be more effective intravenously In order to keep the record straight we must correct the statement often made that Ehrlich claimed to extirpate the infection completely with one injection He definitely did not but he aimed in that direction "I advise therefore that at present we should not use up our strength in looking for new compounds but should concentrate on improving the method of use careful increase of dosage antisepsis repetition of the treatment and the finding of ancillary measures to increase the potency of the drug so that we can always come closer to the principle of the therapia magna sterilisans"

Preceding Ehrlich s discussion is the report of Hata s experiments with 606 in

4 WASSERMANN A NEISSER A, and BRUCK C Eine serodiagnostische Reaction bei Syphilis Deutsche med Wchnschr, 32 745 1906

Jules Bordet and Octave Gengou (Sur l existence de substances sensibilatrices dans la plupart des sérums antimicrobiens Ann Inst Pasteur 15 289 1901) clearly defined the complement fixation reaction using bacterial suspensions as antigens There is no suggestion that they thought of using complement fixation in syphilis perhaps because no antigenic suspension of the causal agent was available Actually they thought at first of complement fixation as a therapeutic method A Wassermann and C Bruck ("Experimentelle Studien uber die Wirkung von Tuberkelbacillen Preparaten auf den tuberculoserkrankten Organismus Deutsche med Wchnschr 32 449 1906) began their complement fixation work giving full credit to Bordet by attempting to demonstrate tuberculin in tuberculous organs A little later in the present paper they applied the method to *syphilis They used as antigen materials presumably* rich in spirochetes namely extracts of organs (liver) of children or fetuses with congenital syphilis the placentas of mothers with secondary syphilis extracts of primary lesions or of condylomata lata or of organs or bone marrow of syphilitic monkeys "The practical importance of these findings is obvious We are in the position to determine on the one hand whether a human serum or an immune serum contains specific antibodies against the incitor of syphilis and we can determine whether a particular organ harbors syphilitic substances But it would be of the greatest diagnostic and therapeutic importance if one could regularly demonstrate syphilitic material or antibodies in the circulating blood of syphilitics This hope was soon realized by the authors with A Schmidt ("Weitere Mitteilungen uber den Nachweis spezifischluetischen Substanzen durch Komplementverankerung" Ztschr f Hyg u Infektionskr 55 451 1906) although they got only 49 positive reactions among 257 "certain" syphilitics At about the same time Wassermann with F Plaut (Ueber das Vorhandensein syphilitischer Antistoffe in der Cerebrospinalflussigkeit von Paralytikern" Deutsche med Wchnschr 32:1769 1906) employed the complement fixation reaction on the spinal fluid of 41 paretics with positive result in 32 Fluids from controls were negative Ladislaus Detre (Ueber den Nachweis von spezifischen Syphilis Antisubstanzen und deren Antigenen bei Luetikern" Wien klin Wchnschr 19 619 1906) published a few weeks after Wassermann and confirmed his findings Wassermann at first clearly regarded the test as immunologically specific in this he was to be disappointed (Ref 5)

5 LANDSTEINER K MULLER R and POTZL, O Zur Frage der Komplementbindungsreaktion bei Syphilis Wien klin Wchnschr 20 1565 1907

Wassermann had thought of his reaction as a test for a specific syphilitic substance but this view was soon to be questioned Leonor Michaelis ("Die Wassermannsche *Syphilisreaktion Berl klin Wchnschr 44 1103 1907)* found that normal liver as well as syphilitic liver gave positive complement fixation with serum of syphilitics although the test was usually weaker with the former Landsteiner and his associates found that alcohol extracts of normal organs such as guinea pig heart served as an adequate antigen for fixing complement with sera of syphilitics This led to an era of lively speculation on the nature of

practice of the treatment of syphilis with Ehrlich s new specific 606 " Lancet, 2:1684 1910) They emphasized the rapid disappearance of spirochetes and they concluded "The importance of the observation lies in the probability that cases of syphilis can be rendered practically non infective in a day or two If this be true Ehrlich will have swept away the scourge of 2000 years "

These papers bring out the optimistic temper of the times as regards a quick cure for syphilis

In the Zeitschrift fur Chemotherapie for 1912 (Vol. 1, Part II Referate) are to be found comprehensive reviews of the American, French Russian Brit ish and Italian literature to date on Salvarsan therapy

8 NOGUCHI Hideyo Cultivation of pathogenic Treponema pallidum J.A.M.A. 57 102, 1911

Noguchi criticized the previous attempts of others to grow pathogenic treponemes in the test tube He described a method of his own whereby he claimed to have accomplished such growth and with two of these culture strains he produced typical syphilis in the rabbit by intra testicular inoculation This note was promptly amplified by a longer article ("A method for the pure cultivation of pathogenic Treponema pallidum [Spirochaeta pallida]" J Exper Med 14 99 1911) with beautiful and convincing plates Noguchi later ("A method for cultivating Treponema pallidum in fluid media" J Exper Med 16 211 1912) described a method for obtaining pure cultures in fluid media which however was not suitable for growth of spirochetes when "they are admixed with con taminating bacteria."

The spirochete is however very difficult to grow and methods have never been adapted for routine practical work. Spirochetes are usually preserved in syphilitic rabbits from whose lymph nodes they can be readily obtained W Kolle and H Schlossberger (Die Persistenz der Syphilisspirochate in Mausen wahrend langer Zeitraume" Deutsche med. Wchnschr 54 129 1928) found that mice which had been inoculated 1½-16 months previously still harbored spirochetes in lymph glands spleen blood and brain as demonstrated by inoculation of other animals with these materials

9 ELLIS Arthur W M Secondary syphilitic meningitis J.A.M.A 53 1263 1912.

It was Paul Ravaut ("Les Réactions nerveuses tardives observé chez certains syphilitiques traités par le Salvarsan," Presse méd 20 181 1912) who raised the vexed question of whether secondary syphilitic meningitis often with cranial nerve involvement (*neurorécidices*) was not promoted by Salvarsan Ellis reviewed the entire literature on early syphilitic meningitis reported 6 cases of his own carefully studied, and concluded "The contention that Salvar san predisposes in any way to development of disease of the nervous system has not yet been established" and he advised further intensive therapy A criti cal discussion of the subject is to be found in Max Nonne *Syphilis und Nervensystem* (3d ed. Berlin S Karger 1915) pp 796 ff

10 GENNERICH [W] Die Resultate der Abortivbehandlung der Syphilis mit Salvarsan bezw kombinierter Behandlung Ztschr f Chemotherap 1, Part II 69 1912

syphilis of the eye and scrotum of rabbits which were completed before the clinical trials These experiments are conclusive—and we quote part of one

X 28-11 Whole cornea opaque great development of blood vessels Weight 3 050 gm Injection of 0 01 gm Salvarsan per kilo of animal intravenously
4 11 Clouding materially less pupil well seen two small vessels
10 11 Cornea entirely clear
30 12 Entirely clear

A somewhat romanticized, but vivid account of Ehrlich and his work is that of Martha Marquart (*Paul Ehrlich* [New York Henry Schuman 1951])

7 NEISSER A and KUZNITZKY E Ueber die Bedeutung des Ehrlich schen Arsenobenzols fur die Syphilisbehandlung Berl klin Wchnschr 7 1485 1910

It is difficult now to appreciate the furor which arose over the prospect of curing syphilis quickly and surely with "606" The German *Wochenschrifte* and a little later journals in other countries were soon filled with brief reports on the results of therapy Neisser s paper is one of the most important early ones "In brief there is no doubt about the eminent action of Arsenobenzol on syphilitic processes The most outstanding effects of mercury and iodides are surpassed Neisser was reserved about occasional failures and thought that perhaps the dose had been too small or that the syphilitic process was in an avascular area "We must advise every syphilitic to seek the new medicine" Meanwhile L Michaelis ("Ueber die Anwendung des Ehrlich Hata schen Syphilismittels in neutraler Suspension" Berl klin Wchnschr 7 1401 1910) the physical chemist, had devised a method for neutralizing the drug so as to render the intramuscular injection painless Later in the year Michaelis ("110 Fälle von Syphilis behandelt nach Ehrlich Hata, *ibid* p 1695) reported extensive clinical trials Interestingly enough Michaelis avoided the intravenous route because he believed the drug to be insoluble at the practically neutral reaction of the blood In regard to the permanence of effect, Michaelis now had three cases which relapsed Meanwhile C Fraenkel and C Grouven ("Erfahrungen mit dem Ehrlichen Mittel 606" Munchen med Wchnschr 57 1771 1910) had a death after intravenous injection, to which Ehrlich himself ("Bietet die intravenose Injection von 606 besondere Gefahren?" Munchen med Wchnschr 57 1826 1910) replied suggesting that it was not the intravenous route but a *hypersensitivity on the part of the patient which was responsible*

Apparently there were no reports on the actual use of 606 in America at this time because at the suggestion of the editor Samuel J Meltzer (Dioxydiaminoarsenobenzol or 606 Ehrlich s newest remedy for syphilis" New York M J 92 371 1910) wrote a general article on the subject 'No matter what qualifications the present statements may have to undergo this great fact is well assured—a single injection of a synthetically made compound is capable of completely sterilizing the diseased animal body in a very short time If reports continue to hold what they promise syphilis could be eradicated from civilized humanity in two or three decades What a hope what a dream!" The first British paper was that of James McIntosh and Paul Fildes ("The theory and

Fever therapy in syphilis especially in late neurosyphilis has been such an important factor in treatment that it deserves mention in the bibliography Wagner v Jauregg as early as 1888 ("Ueber die Einwirkung fieberhafter Erkrankungen auf Psychosen" Jahrb f Psychiat 7 94 1887) noted that in the case reports on so-called recovery from progressive paralysis suppurative lesions were prominent in the history and probably were a factor in healing The present report deals first with treatment of paresis by a mercury iodide "cure" together with old tuberculin In many cases there was a satisfactory remission These results were confirmed by A Pilcz ("Beitrage zur Lehre von progressiven Paralysen" Jahrb f Psychiat. 25 97 1904) However at that time it was thought that suppuration was the important factor Wagner v Jauregg gradually laid more emphasis on fever than on suppuration and got good results by treatment with injections of staphylococcus vaccine in increasing doses with which he stressed both suppuration and fever

Pursuing these ideas further it occurred to Wagner v Jauregg to induce malaria purposefully as a source of fever ("Die Behandlung der progressiven Paralyse and Tabes" Wien med. Wchnschr 71 1106 1210 1921) The use of malaria became a huge discipline in itself all phases of which are authoritatively reviewed by J E Moore (Ref 29 p 374)

Many other methods of inducing fever had their proponents and their vogue foreign protein therapy (M M Kunde George W Hall and F J Gerty "General paralysis the effect of nonspecific protein therapy on the blood and spinal fluid," J.A.M.A 89 1304 1927 [literature]) physical measures such as diathermy (Clarence A Neymann and S L. Osborne "The treatment of dementia paralytica with hyperpyrexia produced by diathermy" J.A.M.A 96 7 1931) hot baths (Jay F Schamberg and Hsien Wu Tseng "Experiments on the therapeutic value of hot baths with special reference to the treatment of syphilis and some physiologic observations" Am J Syph. 2 337 1927 H G Mehrtens and P S Pouppirt, "Hyperpyrexia produced by baths" Arch Neurol. & Psychiat. 22 700 1929 Jay F Schamberg and A. M Rule "Studies of the therapeutic effect of fever in experimental rabbit syphilis" Arch. Dermat. & Syph., 14 243 1928)

14 NOGUCHI Hideyo and MOORE, J W A demonstration of Treponema pallidum in the brain in cases of general paralysis J Exper Med 17 232 1913

Although by this time no one doubted the essentially syphilitic nature of paresis on the basis of history blood Wassermann test and spinal fluid changes it remained for Noguchi clearly to demonstrate the presence of treponemes In the brains of twelve of seventy cases of "undoubted" general paralysis treponemes were demonstrated by a modification of the Levaditi silver method and are pictured in the article Noguchi soon amplified his findings ("Additional studies on the presence of Spirochaeta pallida in general paralysis and tabes dorsalis" J Cutan. Dis 31 543 1913) and reported the demonstration of treponemes in about one fourth of two hundred cases of paresis and tabes Noguchi's work was promptly confirmed by M M G Marinesco and M J Minea ("Présence du Treponema pallidum dans un cas de méningite syphilitique associée à la paralysie générale et dans la paralysie générale" Bull [illegible]

The initial hope of the complete cure of syphilis by one dose of "606" (Ref 6) was soon to be disappointed By 1912 Gennerich for example was giving courses of eight injections at 4-day intervals in some cases followed by a few weeks of iodides and then more Salvarsan, without extirpating the infection It was soon found that the best chance of a quick cure was in seronegative primary patients but that in late cases such a result was not to be expected Homer F Swift and A W M Ellis ("The intensive treatment of syphilis" J.A M.A 59 1251 1912) emphasized the same point and advised combination therapy of *Salvarsan and mercury by the use of which "the relative number of cures* has materially increased" "A reliable rule to follow is four or five intravenous injections of from 0 3 to 0 5 gms with or followed by a course of insoluble mercury intramuscularly After the mercury Salvarsan should again be re peated"

The position is summarized editorially in the Journal of the American Medical Association ("The present position of salvarsan in syphilis" 59 1295 1912)

11 SWIFT Homer F and ELLIS Arthur W M The direct treatment of syphilitic diseases of the central nervous system New York M J 96 53 1912

Swift and Ellis working at the Rockefeller Institute and stimulated by Flexner s direct application of serum to the subarachnoid space in meningitis conceived the idea of a similar procedure in neurosyphilis In preliminary experiments with monkeys (Arthur W M Ellis and Homer F Swift, "The effect of intraspinous injections of Salvarsan and Neosalvarsan in monkeys" J Exper Med 18 428 1913) they found that even small amounts of Salvarsan were excessively irri tating as had others in the literature which is reviewed They resorted there fore to intravenous injection of Salvarsan following which the patient was bled and 30 cc of serum diluted with saline were injected intraspinally They found that the serum of patients treated with Salvarsan had an increased spiro cheticidal action (Swift and Ellis "A study of the spirocheticidal action of the serum of patients treated with Salvarsan *ibid* p 435) and they also believed that their patients were improved This was the so-called "Swift Ellis" treatment which had a tremendous vogue and was a precursor of many variations of intra spinal therapy all now obsolete

12 SCHREIBER E Ueber Neosalvarsan Munchen med Wchnschr 59 905 1912

By this time various shortcomings of the old Salvarsan were recognized Ehrlich had now brought out his 914th compound which was commercially designated as "Neosalvarsan" The principal claim for the new drug was that it was less toxic than the old Schreiber concludes that the advantages of Neosalvarsan are "(1) *its easy solubility at absolutely neutral reaction* (2) *it is better tolerated* and can therefore be given in larger doses (3) its effect is at least as good as that of the old Salvarsan (4) the material lends itself better to intramuscular injection"

13 JAUREGG Wagner v *Uber Behandlung der progressiven Paralyse mit* Bacterientoxinen Wien klin Wchnschr 25 61 1912

Fever therapy in syphilis especially in late neurosyphilis has been such an important factor in treatment that it deserves mention in the bibliography Wagner v Jauregg as early as 1888 (Ueber die Einwirkung fieberhafter Erkrankungen auf Psychosen " Jahrb f Psychiat 7:94 1887) noted that in the case reports on so-called recovery from progressive paralysis suppurative lesions were prominent in the history and probably were a factor in healing The present report deals first with treatment of paresis by a mercury iodide "cure" together with old tuberculin In many cases there was a satisfactory re mission These results were confirmed by A Pilcz ("Beitrage zur Lehre von progressiven Paralysen " Jahrb f Psychiat 25:97 1904) However, at that time it was thought that suppuration was the important factor Wagner v Jauregg gradually laid more emphasis on fever than on suppuration and got good results by treatment with injections of staphylococcus vaccine in increas ing doses with which he stressed both suppuration and fever

Pursuing these ideas further it occurred to Wagner v Jauregg to induce malaria purposefully as a source of fever ("Die Behandlung der progressiven Paralyse and Tabes " Wien med Wchnschr 71 1106 1210 1921) The use of malaria became a huge discipline in itself all phases of which are authori tatively reviewed by J E Moore (Ref 29 p 374)

Many other methods of inducing fever had their proponents and their vogue foreign protein therapy (M M Kunde George W Hall and F J Gerty "Gen eral paralysis the effect of nonspecific protein therapy on the blood and spinal fluid " J A M A 89 1304 1927 [literature]) physical measures such as dia thermy (Clarence A Neymann and S L Osborne "The treatment of dementia paralytica with hyperpyrexia produced by diathermy " J A M A 96 7 1931) hot baths (Jay F Schamberg and Hsien Wu Tseng "Experiments on the thera peutic value of hot baths with special reference to the treatment of syphilis and some physiologic observations " Am J Syph 2 337 1927 H G Mehrtens and P S Pouppirt "Hyperpyrexia produced by baths " Arch Neurol & Psychiat 22 700 1929 Jay F Schamberg and A M Rule "Studies of the therapeutic effect of fever in experimental rabbit syphilis " Arch Dermat & Syph 14 243 1926)

14 NOGUCHI Hideyo and MOORE J W A demonstration of Treponema pallidum in the brain in cases of general paralysis J Exper Med 17 232 1913

Although by this time no one doubted the essentially syphilitic nature of paresis on the basis of history blood Wassermann test and spinal fluid changes it remained for Noguchi clearly to demonstrate the presence of treponemes In the brains of twelve of seventy cases of "undoubted general paralysis trepo nemes were demonstrated by a modification of the Levaditi silver method and are pictured in the article Noguchi soon amplified his findings ("Additional studies on the presence of Spirochaeta pallida in general paralysis and tabes dorsalis " J Cutan Dis 31 543 1913) and reported the demonstration of treponemes in about one fourth of two hundred cases of paresis and tabes Noguchi s work was promptly confirmed by M M G Marinesco and M J Minea ("Presence du Treponema pallidum dans un cas de méningite syphili tique associée à la paralysie générale et dans la paralysie générale Bull Acad

The initial hope of the complete cure of syphilis by one dose of 606 (Ref 6) was soon to be disappointed By 1912 Gennerich for example was giving courses of eight injections at 4-day intervals in some cases followed by a few weeks of iodides and then more Salvarsan without extirpating the infection It was soon found that the best chance of a quick cure was in seronegative primary *patients but that in late cases such a result was not to be expected* Homer F Swift and A W M Ellis ("The intensive treatment of syphilis" J A M A 59 1251 1912) emphasized the same point and advised combination therapy of Salvarsan *and* mercury by the use of which "the relative number of cures has materially increased" "A reliable rule to follow is four or five intravenous injections of from 0 3 to 0 5 gms with or followed by a course of insoluble mercury intramuscularly After the mercury Salvarsan should again be repeated

The position is summarized editorially in the Journal of the American Medical Association ("The present position of salvarsan in syphilis" 59 1295 1912)

11 SWIFT Homer F and ELLIS Arthur W M The direct treatment of syphilitic diseases of the central nervous system New York M J 96 53 1912

Swift and Ellis working at the Rockefeller Institute and stimulated by Flexner s direct application of serum to the subarachnoid space in meningitis conceived the idea of a similar procedure in neurosyphilis In preliminary experiments with monkeys (Arthur W M Ellis and Homer F Swift "The effect of intraspinous injections of Salvarsan and Neosalvarsan in monkeys" J Exper Med 18 428 1913) they found that even small amounts of Salvarsan were excessively irritating as had others in the literature, which is reviewed They resorted therefore to intravenous injection of Salvarsan following which the patient was bled and 30 cc. of serum diluted with saline were injected intraspinally They found that the serum of patients treated with Salvarsan had an increased spirocheticidal action (Swift and Ellis "A study of the spirocheticidal action of the serum of patients treated with Salvarsan" *ibid* p 435) and they also believed that their patients were improved This was the so called "Swift Ellis" treatment which had a tremendous vogue and was a precursor of many variations of intra spinal therapy all now obsolete

12 SCHREIBER E Ueber Neosalvarsan Munchen med Wchnschr 59 905 1912

By this time various shortcomings of the old Salvarsan were recognized Ehrlich had now brought out his 914th compound which was commercially designated as Neosalvarsan" The principal claim for the new drug was that it was less toxic than the old Schreiber concludes that the advantages of Neosalvarsan are "(1) its easy solubility at absolutely neutral reaction (2) it is better tolerated and can therefore be given in larger doses (3) its effect is at least as good as that of the old Salvarsan (4) the material lends itself better to intramuscular injection"

13 JAUREGG Wagner v Über Behandlung der progressiven Paralyse mit Bacterientoxinen Wien klin Wchnschr 25 61 1912

prevented general dissemination of the disease Brown and Pearce studied this point by excising at various intervals after scrotal inoculation the inguinal lymph nodes of rabbits and testing for spirochetes by injecting the excised nodes into other animals In a series of twenty three animals tested at intervals of from 2 to 5 days after inoculation it was uniformly found that spirochetes were present in the regional lymph nodes an indication of definite spread of the organisms even before the appearance of the primary lesion Furthermore as early as 1 week after injection blood withdrawn from the heart contained enough spirochetes to produce syphilis when injected into the testes of other rabbits Finally despite excision of the scrotum and testes 48 hours after inoculation all the animals developed syphilitic lesions "It would appear therefore that for practical purposes there is no appreciable time during which a syphilitic lesion can be regarded as confined to the focus of entry"

18 SAZERAC R and LEVADITI C Traitement de la syphilis par le bismuth Compt rend Acad d sc. **173**:338 1921

The writers after having experimented with sodium and potassium bismuth tartrate in experimental syphilis of rabbits ("Action du bismuth sur la syphilis et sur la trypanosomiase du Nagana" *ibid* 172 1391 1921) report five cases of syphilis treated with this preparation by intramuscular injection There was rapid (2–3 days) disappearance of spirochetes and healing of the lesions in about a week Gummata also healed and became scarred Bismuth immediately became popular and innumerable preparations soluble and insoluble were thrown on the market The subject is summarized in Moore (Ref 29 p 134) with bibliography Perhaps the most important American work on the subject was that of Hanzlik and his associates (P J Hanzlik and H G Mehrtens Comparative excretion and absorption of different bismuth products" Arch Dermat. & Syph **22**:861 1930 P J Hanzlik, H G Mehrtens C Gurchot and C C Johnson "Iodobismitol" J A M A **98** 537 1932 see also W F von Oettingen "The absorption distribution and excretion of bismuth" Physiol. Rev **10** 222 1930)

After having a tremendous vogue and having practically replaced mercury in the treatment of syphilis bismuth is now in the penicillin era little used

19 KOLLE W Experimentelle Untersuchungen uber die "Abortivheilung der Syphilis Deutsche med Wchnschr **48** 1301 1922

The problems of immunity in syphilis which perplexed the older clinicians are not yet fully solved today It is impossible to refer in detail to the huge literature all we can do is to pick out certain key pieces of work

Kolle set himself the problem of finding out whether it was possible to achieve a biological cure of experimental syphilis in rabbits and if so how long after infection one might begin treatment and still produce a cure He had found that infected untreated rabbits could not be "reinfected after 90 days whereas the earlier reinoculation was practiced the more frequently reinfection was possible He concluded that a syphilitic man is like the rabbit proof against reinfection because he still harbors spirochetes But if some balance is upset syphilitics may suffer years later from the renewed activity of their own organisms (gummata) Kolle assumed reinfection to be evidence of biological cure with extirpation of all spirochetes He treated rabbits with experimental

de méd Paris 69 235 1913) but in only one of twenty four cases of general paralysis

15 ELLIS Arthur W M and SWIFT Homer F The cerebrospinal fluid in syphilis J Exper Med 18 162 1913

Swift and Ellis after reviewing the literature report systematic studies of the spinal fluid in 113 cases of syphilis of all types Pressure cell counts globulin and Wassermann were all done *Of special importance was the finding in several interesting cases of secondary syphilis of slightly increased cell count and globulin* They conclude with these now well recognized recommendations "The diagnosis of any syphilitic condition of the central nervous *system is* not complete without an examination of the spinal fluid and in the treatment of these conditions repeated examinations of the fluid furnish the best guide to therapy A negative Wassermann reaction in the blood is no evidence that the nervous system is not affected and every patient with increased cells globulin or a positive Wassermann reaction *in the* spinal *fluid* needs active antisyphilitic treatment No patient who has been infected with syphilis can conscientiously be discharged as cured until the spinal fluid has been examined and found normal *even though he remains free from signs* and *symptoms and* has a persistently negative Wassermann reaction in the blood Authoritative discussions of the spinal fluid in neurosyphilis with a review of the literature are those of Max Nonne in *Syphilis und Nervensystem* (2d ed Berlin S Karger 1909) pp 607 ff and of Bernhard Dattner *The Management of Neurosyphilis* (New York Grune & Stratton 1944)

16 BROWN Wade H and PEARCE Louise Experimental syphilis in the rabbit I Primary infection of the testicle J Exper Med 20 475 1920

Parodi (Umberto Parodi Ueber die Uebertragung der Syphilis auf den Hoden des Kaninchens" Centralbl f Bakt. 44 428 1907) inserted a small bit of a syphilitic papule under the tunica vaginalis of the testis of a rabbit on May 11 On June 9 the animal was killed and a round cell infiltration and numerous spirochetes were found under the microscope *This method of testicular inoculation* has become a standard one in studying syphilitic infection and immunity The extensive early work on the rabbit is fully summarized by P Uhlenhuth and P Mulzer ("*Beiträge zur experimentellen* Pathologie und Therapie der Syphilis mit besonderen Berucksichtigung der Impf Syphilis der Kaninchen" Arb a d k Gsndhtsamte 44 307 1913) in a classical monograph which includes numerous experiments of their own on every phase of experimental syphilis in rabbits and monkeys

Brown and Pearce made *elaborate studies of experimental rabbit syphilis* but this paper is especially important as the first of a long series on experimental infection and immunity many of which are to be found in the Journal of Experimental Medicine for 1920–22

17 BROWN Wade H and PEARCE Louise A note on the dissemination of Spirochaeta pallida from the primary focus of infection Arch Dermat & Syph *N S 2 470 1920*

The question of how quickly the virus of syphilis spreads after inoculation is an old one which vexed the early therapists in deciding whether excision of chancre

21 BROWN Wade H and PEARCE Louise Tryparsamide its action and uses J A M A 82 5 1924

The properties of this drug were first described by W A Jacobs and Michael Heidelberger ("Chemotherapy of trypanosome and spirochete infections I N phenylglycine amide p arsonic acid" J Exper Med 30 417 1919) Differing from the arsphenamines in being a pentavalent instead of a trivalent arsenic compound it appeared to be of very low toxicity and could be given to animals in large doses (Wade H Brown and Louise Pearce "Chemotherapy of trypanosome and spirochete infections biological series I The toxic action of N phenylglycine-amide-p-arsonic acid J Exper Med 30:417 1919) until retrobulbar neuritis was found to be a fairly frequent result (L L Sloan and A C Woods "The effect of tryparsamide on the eye a clinical study of the objective ocular reaction" Am J Syph 20:583 1936) In the present paper Brown and Pearce give a critical summary of the actions and uses of the drug Meanwhile W F Lorenz A S Loewenhart W J Blackwenn and F J Hodges ("The therapeutic uses of tryparsamide in neurosyphilis" J A M A 80:1487 1923) emphasized its special value in neurosyphilis The drug is fully discussed in Moore s book (Ref 29)

22 CHESNEY Alan M and KEMP Jarold E Studies in experimental syphilis III Further observations on the possibility of cure of syphilis in the rabbit with arsphenamine J Exper Med 43 17 1925

The elaborate studies of Chesney and his associates followed those of Brown and Pearce (Ref 16) Chesney found that syphilitic rabbits can be treated with arsphenamine in such a manner as to render the lymph nodes incapable of transmitting the infection to normal rabbits even if treatment is begun late in the course of the disease Those treated late in spite of apparent cure were almost uniformly refractory to a second infection Chesney felt contrary to earlier ideas that this refractory state could be explained by the existence of acquired immunity which persists after abolition of the disease rather than by the persistence of first infection

Chesney summarized his views on immunity in syphilis (Alan M Chesney "Acquired immunity in syphilis" Am J Syph 14 289 1930) as follows "I think of acquired immunity in syphilis as a state of resistance which evolves comparatively slowly and at its best is not always complete general in its distribution but imparted to some tissues more than to others but not necessarily dependent upon the persistence of infection for its maintenance"

Chesney and Kemp ("The curability of syphilis" J A M A 88 905 1927) later emphasized the method of inoculating rabbits with lymph nodes from human patients as a test for cure

Chesney summarizes the whole question of immunity in syphilis to date in his monograph of 1926 (Ref 24)

23 MOORE Joseph Earle and KEIDEL Albert The treatment of early syphilis I A plan of treatment for routine use Bull Johns Hopkins Hosp 39 1 1926

At the end of the nineteenth century a feeling grew up among syphilologists that it was important to continue treatment after clinical manifestations had disappeared in order to obtain a real cure This feeling became a conviction

syphilis with three large doses of Salvarsan 3 15 20 25 30 45 60 90 and 120 days after infection After an interval of over 90 days had elapsed in each animal he applied the test of complete cure by attempting to reinoculate The results were striking Up to 45 days after the original infection it was usually possible to sterilize the animal but after 45 days only an occasional rabbit developed chancre on later reinoculation These experiments had great repercussions on human therapeutic practice It is of interest that the older clinicians had observed that partial treatment might be worse than none and that they often advised that the secondaries be allowed to appear before therapy was started with mercury In other words if complete sterilization is possible by early intensive treatment it should be conscientiously practiced, but partial subcurative therapy in the early stages might simply interfere with development of the patient s own immunity and therefore be worse than none These experiments on the importance of early intensive therapy influnced clin ical practice for years to come

Meanwhile Wade H Brown and Louise Pearce ("Superinfection in experi mental syphilis following the administration of subcurative doses of Arsphena mine or Neoarsphenamine," J Exper Med 33 553 1921) came to somewhat different conclusions "namely that subcurative treatment of animals with marked primary lesions of the testicles altered their resistance to such an extent as to render them susceptible to a second cutaneous infection without having effected a cure of the original infection

Along this line Brown and Pearce (Experimental production of clinical types of syphilis in the rabbit Arch Dermat & Syph 3 254 1921) found that, by modifying the course of the infection as for example by castration or subcurative therapy whereas the syphilitic lesions as a rule remained localized in the controls almost all the treated animals showed generalized lesions involving eye mucous membranes periosteum bone and skin The conclusion seemed justified that the ordinary progress of syphilis is bound up with immu nity reactions which are capable of modification by spontaneous or by externally regulated influences Such considerations as these are obviously most important in therapy

20 PEARCE Louise and BROWN Wade H A study of the relation of Treponema pallidum to lymphoid tissues in experimental syphilis J Exper Med 35 39 1922

Having demonstrated (Ref 17) the wide dissemination of spirochetes in rab bits before clinical signs appear Brown and Pearce made studies to determine their possible persistence in animals which had spontaneously recovered and had remained well for considerable periods of time They excised popliteal lymph nodes from these animals and reinjected the emulsified glands into the testes of other rabbits Six rabbits were studied which had been infected for 7–51 months and in which the clinical latent period was of at least 3 months duration In the excised nodes of all these animals it was possible to demon strate spirochetes capable of producing disease From these facts it may be concluded that rabbits which have recovered from clinical syphilis may harbor virulent spirochetes almost indefinitely even though no further manifestations of infection occur

in some patients at all stages of the disease it was surprising that in many individuals "resistance factors" sufficed "not only to hold the infection in check but to fully overcome it." Bruusgaard's actual figures were approximately as follows no clinical or serological evidence of disease 25 per cent dead of other cause than syphilis 25 per cent positive serology only 15 per cent syphilis of skin mucous membrane or bone 12 per cent cardiovascular syphilis 12 per cent neurosyphilis 9 5 per cent Moore and his group (J E Moore H N Cole P A O'Leary J H Stokes U J Wile T Parran Jr and L. J Usilton "Cooperative clinical studies in the treatment of syphilis" Ven Dis Inform 13 351 1932) also estimate that spontaneous "cure" occurs in 25–35 per cent of untreated syphilitics whereas in another 25–35 per cent all that is demonstrable is a positive Wassermann reaction J J Peters J H Peers S Olansky J C Cutler and G A Gleeson ("Untreated syphilis in the male Negro" J Chronic Dis 1:127 1955) emphasize the frequency of cardiovascular and neurosyphilis at autopsy in untreated male Negroes The subject is well summarized by Hugh J Morgan "The prognosis of syphilis" J.A.M.A. **112** 311 1939

It is of interest that Danholt and his colleagues (N Danholt E G Clark, and F Gjestland "The Oslo-study of untreated syphilis a re-study of the Boeck Bruusgaard material concerning the fate of syphilitics who receive no specific treatment a preliminary report," Acta dermat. venereol. **34** 34 1954) have recently restudied Bruusgaard's material.

26 TATUM A. L. and COOPER, G A An experimental study of mapharsen (meta amino para hydroxy phenyl arsine oxide) as an antisyphilitic agent J Pharmacol & Exper Therap **50** 198 1934

This drug, described by Ehrlich (Ref 6) was revived by Tatum and Cooper thoroughly tested in animals and recommended for clinical trial They point out that mapharsen is a pure chemical, whereas the arsphenamines are chemical mixtures which vary with each lot and therefore require biological assay Mapharsen became popular enough to replace the arsphenamines in the treatment schemes of many American clinics Mapharsen as well as other arsenicals are thoroughly discussed in J E. Moore's book (Ref 29)

27 STOKES John H and GARNER Vaughan C Public health problems methods and policy in the control of syphilis Am. J.M Sc. **194** 578 1937

We cannot in this bibliography go into the public health aspects This authoritative review is to be mentioned however as an introduction to this phase of the subject.

28 REIN Charles R WISE Fred and CUKERBAUM Alfred R. The control and prevention of transfusion syphilis J.A.M.A **111** 13 1938

The authors refer to the first reported case of transfusion syphilis (John A Fordyce "Some problems in the pathology of syphilis" Am. J M Sc. **149** 781 1915) and point out that while only 68 proved cases of syphilis transmitted by transfusions have been reported, the total number is obviously greater They

when it was found that a single dose of Salvarsan did not necessarily cure and when it was felt that reversal of Wassermann reaction was an obligatory criterion Treatment became longer and longer, doctors began to insist on a full year and innumerable treatment schedules were devised Moore and Keidel pointed out that full curative treatment was especially necessary in early syphilis whereas in late syphilis it was more important to control the presenting lesions They developed an organized definitive plan of therapy consisting essentially of 70 weeks of continuous therapy with alternating courses of arsphenamine and bismuth This general plan of therapy remained in vogue until the advent of penicillin They summarized their principles as follows

"That treatment shall be *continuous* consisting of courses of arsphenamine alternating with courses of mercury by inunction (or of insoluble bismuth salts intramuscularly) plus potassium iodide that treatment be carried out under full serological control that treatment shall be prolonged without intermission for one year after the blood and spinal fluid have become and have remained completely negative"

Interestingly enough, just before penicillin became available there was under study (H T Hyman L Chargin J L Rice and W Leifer Massive dose chemotherapy of early syphilis by the intravenous drip method" J A M A 113 1208 1939) a quick method of cure of early syphilis by continuous intravenous infusion of arsphenamine in dextrose at the rate of 1 500 cc of 5 per cent glucose containing 1 gm of arsphenamine in 15 hours The co operating clinics of New York and midwestern groups ("Massive arsenotherapy for syphilis J A M A 126 554 1944) reviewed the therapeutic results in 4 351 cases and found a satisfactory outcome in 85-90 per cent of primary syphilis and 70 per cent of secondary syphilis

24 CHESNEY Alan M Immunity in syphilis Medicine 5:375 1926

Before the discovery of the spirochete it was recognized that reinfection in syphilis was very infrequent, and certain other crude facts of immunity were dimly sensed However no sooner had transmission of the disease to animals been achieved and the causal organism been demonstrated than there appeared a great flood of work on experimental syphilis and immunity Early important summaries of much of this material are to be found in A Neisser *Beitrage zur Pathologie und Therapie der Syphilis* (Berlin Julius Springer 1911) The monograph of Chesney is however a landmark definitive to date A late authoritative review of the subject is that of C Bruck "Immunitat bei Syphilis" in W Kolle and A von Wassermann *Handbuch der pathogenen Microorganismen* (Jena Gustav Fischer 1930) 7 155 Harold J Magnuson wrote an excellent recent summary "Current concepts of immunity in syphilis" Am J Med 5 641 1948

25 BRUUSGAARD E Ueber das Schicksal der nicht spezifisch behandelten Luetiker Arch f Dermat u Syph 157 309 1929

The early nineteenth-century physicians often questioned the value of mercurial treatment of syphilis but they had no adequate follow up of their untreated cases Bruusgaard reports on patients first seen in the clinic between 1889 and 1910 who received no specific therapy Although lesions occurred

in some patients at all stages of the disease It was surprising that in many individuals "resistance factors" sufficed "not only to hold the infection in check but to fully overcome it" Bruusgaard's actual figures were approximately as follows no clinical or serological evidence of disease 25 per cent dead of other causes than syphilis 25 per cent positive serology only 15 per cent syphilis of skin mucous membrane or bone 12 per cent cardiovascular syphilis 12 per cent neurosyphilis 9 5 per cent Moore and his group (J E Moore H N Cole P A O'Leary J H Stokes U J Wile T Parran, Jr and L J Usilton "Cooperative clinical studies in the treatment of syphilis" Ven Dis Inform., 13:351 1932) also estimate that spontaneous "cure" occurs in 25–35 per cent of untreated syphilitics whereas in another 25–35 per cent all that is demonstrable is a positive Wassermann reaction J J Peters J H Peers S Olansky J C Cutler and G A Gleeson ("Untreated syphilis in the male Negro" J Chronic Dis 1:127 1955) emphasize the frequency of cardiovascular and neurosyphilis at autopsy in untreated male Negroes The subject is well summarized by Hugh J Morgan "The prognosis of syphilis" J A M.A 112:311 1939

It is of interest that Danholt and his colleagues (N Danholt E C Clark, and F Gjestland "The Oslo-study of untreated syphilis a re-study of the Boeck Bruusgaard material concerning the fate of syphilitics who receive no specific treatment a preliminary report," Acta dermat. venereol 34:34 1954) have recently restudied Bruusgaard's material

26 TATUM A L and COOPER, C A An experimental study of mapharsen (meta amino para hydroxy phenyl arsine oxide) as an antisyphilitic agent J Pharmacol & Exper Therap 50:198 1934

This drug, described by Ehrlich (Ref 6) was revived by Tatum and Cooper thoroughly tested in animals and recommended for clinical trial They point out that mapharsen is a pure chemical, whereas the arsphenamines are chemical mixtures which vary with each lot and therefore require biological assay Mapharsen became popular enough to replace the arsphenamines in the treatment schemes of many American clinics Mapharsen as well as other arsenicals are thoroughly discussed in J E Moore's book (Ref 29)

27 STOKES John H and GARNER Vaughan C Public health problems methods and policy in the control of syphilis Am. J M Sc 194 578 1937

We cannot, in this bibliography go into the public health aspects This authoritative review is to be mentioned however as an introduction to this phase of the subject

28 REIN Charles R WISE Fred and CUKERBAUM Alfred R The control and prevention of transfusion syphilis J.A M A 111:13 1938

The authors refer to the first reported case of transfusion syphilis (John A Fordyce "Some problems in the pathology of syphilis Am J M Sc 149:781 1915) and point out that while only 68 proved cases of syphilis transmitted by transfusions have been reported the total number is obviously greater They

make a plea for rigid serological tests on all donors[a] In these cases following transfusion there is no visible primary lesion but the first clinical manifestations are "secondaries"

29 MOORE Joseph Earle The modern treatment of syphilis 2d ed Springfield Charles C Thomas 1941 also 1st ed 1933

In this monumental book of nearly seven hundred pages Moore discusses authoritatively and in detail every facet of the treatment of syphilis in the pre penicillin era Extensive bibliographies are given The book is a definite landmark in the history of the subject

30 MAHONEY John F, ARNOLD R C and HARRIS A Penicillin treatment of early syphilis a preliminary report Ven Dis Inform 24 355 1943 also Am J Pub Health 33 1387 1943

The writers decided to try penicillin in syphilis "after limited animal experimentation indicated that penicillin possessed some spirochetiadal activity" Four patients with primary lesions were treated with 25 000 units of the drug intramuscularly at 4 hour intervals night and day for 8 days The chancres all became dark field negative within 16 hours Various serological tests rapidly became negative It was of interest that during the first 8 hours of therapy the patients complained of malaise and headache and had slight elevations of temperature The lesions became painful and the regional lymph nodes were enlarged and tender Mahoney's observations were promptly confirmed by C W Barnett (Arthur L Bloomfield Lowell A Rantz and William M M Kirby "The clinical use of penicillin" J A M A, 124 627 1944) who reported similar results in 7 cases of early syphilis Mahoney (J F Mahoney R C Arnold Burton L Sterner A Harris and M R Zwally "Penicillin treatment of early syphilis II" J A M A 126 63 1944) soon reported a follow up study of their original patients and in 1946 the Committee on Medical Research of the National Research Council and the United States Public Health Service issued a joint statement ("The treatment of early syphilis with penicillin J A M A 131 265 1946) in which it was pointed out that there were some treatment failures, especially in those treated late and in those treated with a total of only 600 000 units as against 2 400 000 units of penicillin

31 STOKES John H BEERMAN Herman and INGRAHAM Norman R Jr Modern clinical syphilology—diagnosis treatment case study 3d ed Philadelphia and London W B Saunders Co 1944

A tremendous treatise which covers the entire field of clinical syphilis up to the penicillin era

32 MOORE Joseph Earle Penicillin in syphilis Springfield Charles C Thomas 1946

The early reports were followed by a flood of studies of such dimensions that by 1946 Moore felt impelled to summarize them together with his own con

[a] Yet this obviously does not replace careful history and physical examination We have seen one case in which transfusion from a man in the primary seronegative stage transmitted a violent syphilitic infection to the recipient—his father

clusions in book form This compilation is definitive to date and deals with penicillin in every stage of syphilis with extensive bibliographies By 1953 the same writer (J E Moore "The changing pattern of syphilis 1941–1953" Am Int Med 39:641 1953) was able to state that "penicillin first introduced into the treatment of syphilis in 1943 has now completely replaced arsenic bismuth and mercury in all stages of syphilis" A C Curtis D K Kitchen P A O'Leary H Ratner C R Rein A G Shoch L W Shaffer and U J Wile (Penicillin treatment of syphilis" J A M A 145 1223 1951) also summarize methods and results of penicillin therapy in various stages of syphilis

33 NELSON Robert A Jr and MAYER Manfred M Immobilization of Treponema pallidum in vitro by antibody produced in syphilitic infection J Exper Med 89 369 1949

As a tool for studying immunity in syphilis the writers sought a serological test more specific than the usual complement fixation or precipitin tests for "reagin They were able to extract from the testes of rabbits with acute syphilitic orchitis a heavy suspension of motile treponemes By adding appropriate quantities of serum from syphilitic people and animals together with complement most of the treponemes were rendered immobile in the dark field in contrast to normal sera which in control tests did not interfere with the motility of treponemes They feel that this procedure—the treponemal immobilization test—is a test for specific syphilitic antibody Nelson and his associates soon published further studies (A S Khan R A Nelson Jr and T B Turner "Immunological relationships among species and strains of virulent treponemes as determined with the treponemal immobilization test" Am J Hyg 53:296 1951 R A Nelson Jr H E C Zhenthn J A Diesendruck and P G M Austin Jr "Studies on treponemal immobilizing antibodies in syphilis incidence in serum and cerebrospinal fluid in human beings and absence in 'biologic false positive reactors" Am J Syph 34 101 1950 R A Nelson Jr and J A Diesendruck "Studies on treponemal immobilization antibodies in syphilis I Techniques of measurement and factors influencing immobilization" J Immunol 66 667 1951) Nelson s work was soon confirmed by others (J L Miller M H Slatkin R R Feiner J Portnoy and A B Cannon "Treponemal immobilization test reliability of results for the diagnosis of syphilis J A M A 149 987 1952) who found no false positives with the test, but an occasional negative "after a certain time in patients who have had syphilis particularly if adequate treatment was given in the early stages J L Miller M H Slatkin M Brodey H L Wechsler and J H Hill ("Studies with the treponemal immobilizing test" J A M A 154:1241 1954) report an extensive experience with the test and they emphasize its specificity and value in ruling out false positives It is improbable that this valuable test will soon be available for "routine use However it is invaluable as a tool for immunological studies and is obtainable in many places for special human case A clear simple statement about the procedure is made by C W Barnett "The treponemal immobilization test in the diagnosis of syphilis" Stanford M Bull 9 205 1951

34 MOORE J E and MOHR C F Biologically false positive serologic tests for syphilis type incidence and cause J A M A 150 467 1952

make a plea for rigid serological tests on all donors [2] In these cases following transfusion there is no visible primary lesion but the first clinical manifestations are "secondaries"

29 MOORE, Joseph Earle The modern treatment of syphilis 2d ed Springfield Charles C Thomas 1941 also 1st ed 1933

In this monumental book of nearly seven hundred pages Moore discusses authoritatively and in detail every facet of the treatment of syphilis in the pre penicillin era Extensive bibliographies are given The book is a definite landmark in the history of the subject

30 MAHONEY John F ARNOLD R C and HARRIS A Penicillin treatment of early syphilis a preliminary report Ven Dis Inform 24 355 1943, also Am J Pub Health, 33 1387 1943

The writers decided to try penicillin in syphilis "after limited animal experimentation indicated that penicillin possessed some spirocheticidal activity" Four patients with primary lesions were treated with 25 000 units of the drug intramuscularly at 4 hour intervals night and day for 8 days The chancres all became dark field negative within 16 hours Various serological tests rapidly became negative It was of interest that during the first 8 hours of therapy the patients complained of malaise and headache and had slight elevations of temperature The lesions became painful and the regional lymph nodes were enlarged and tender Mahoney's observations were promptly confirmed by C W Barnett (Arthur L Bloomfield Lowell A Rantz and William M M Kirby The clinical use of penicillin J A M A 124 627, 1944) who reported similar results in 7 cases of early syphilis Mahoney (J F Mahoney R C Arnold Burton L Sterner A Harris and M R Zwally Penicillin treatment of early syphilis II" J A M A 126 63 1944) soon reported a follow up study of their original patients and in 1946 the Committee on Medical Research of the National Research Council and the United States Public Health Service issued a joint statement ("The treatment of early syphilis with penicillin J A M A 131 265 1946) in which it was pointed out that there were some treatment failures especially in those treated late and in those treated with a total of only 600 000 units as against 2 400 000 units of penicillin

31 STOKES John H BEERMAN Herman and INGRAHAM Norman R Jr Modern clinical syphilology—diagnosis treatment case study 3d ed Philadelphia and London W B Saunders Co 1944

A tremendous treatise which covers the entire field of clinical syphilis up to the penicillin era

32 MOORE Joseph Earle Penicillin in syphilis Springfield Charles C Thomas 1946

The early reports were followed by a flood of studies of such dimensions that by 1946 Moore felt impelled to summarize them together with his own con

[2] Yet this obviously does not replace careful history and physical examination We have seen one case in which transfusion from a man in the primary seronegative stage transmitted a violent syphilitic infection to the recipient—his father

A world wide questionnaire was sent out to syphilis clinics inquiring about their current methods of treating early syphilis Two hundred and seventy seven replies were received from 55 countries giving particulars of 291 schedules A total of 65 3 per cent of the participants used penicillin alone and 28 9 per cent used it in combination with other drugs Penicillin alone was used especially in North American clinics The paper is full of interesting details and charts which must be consulted James K Shafer Lida J Usilton and Eleanor V Price ("Long term studies of results of penicillin therapy in early syphilis" Bull World Health Organ 10:563 1954) came to the conclusion in a follow up study that 4 800 000 units of penicillin were desirable for the treatment of early syphilis and at the sixth year following penicillin treatment satisfactory results were recorded in 98–99 per cent of the patients with primary and secondary syphilis J K Shafer and C A Smith ("Treatment of early infectious syphilis with N_1N-dibenzylethylenediamene dipenicillin G Bull World Health Organ 10 619 1954) also found that 2 500 000 units of this depository penicillin in one injection seemed to prove equally as effective as 4 800 000 units of procaine penicillin and aluminum monostearate (P A M) for the treatment of early syphilis

38 HARDY Paul H Jr and NELL, E Ellen Specific agglutination of Treponema pallidum by sera from rabbits and human beings with treponema infections J Exper Med 101:367 1955

The writers refer to the work of T B Turner ("Protective antibodies in the serum of syphilitic rabbits" J Exper Med 69:867 1939) who first demonstrated, by neutralization experiments in rabbits the development of *specific* immunity in treponemal infections Turner s method was however too complicated and cumbersome for general use Hardy and Nell were able to prepare suspensions of *Treponema pallidum* suitable for specific agglutination studies and capable of being stored for months By means of such studies they demonstrated true syphilitic antibodies different from "non specific" Wassermann antibody This test like the treponemal immobilization test (Ref 33) is highly specific

Ever since the early days of the Wassermann test it has been known that false positive tests might be obtained Moore and his associates have recently made systematic studies of this phenomenon and have designated as biologically false positives those which were not due to technical errors They distinguish between acute and chronic BFP reactors The "acute variety is a temporary phenomenon which occurs especially in connection with various acute infectious diseases and usually disappears spontaneously within 6 months The "chronic" variety on the other hand is not associated with any evident acute cause and the standard serodiagnostic test remains positive indefinitely This type has recently been comprehensively dealt with by Moore and Lutz (Joseph Earle Moore and W Beale Lutz "The natural history of systemic lupus erythematosus an approach to its study through chronic biologic false positive reactors" J Chronic Dis 1 297 1955)

35 HOLLANDER David H TURNER Thomas B and NELL E Ellen The effect of long continued subcurative doses of penicillin during the incubation period of experimental syphilis Bull Johns Hopkins Hosp 90 105 1952

The introduction of penicillin made necessary a re-evaluation of immunity factors in connection with penicillin therapy In this important study for example it was found that subcurative doses of penicillin prolonged the incubation period In some rabbits the incubation period was prolonged up to 2 weeks by means of subclinical infection but then "the evolution of the syphilitic infection after termination of treatment was in general similar to that observed in untreated animals Wholly symptomless infection was not observed Rabbits were either cured or subsequently developed clinically recognizable lesions" The implication is clear that in man it is better to waste some penicillin than to give too little in both prophylaxis and therapy

36 BARNETT C W EPSTEIN Norman N BREWER A Frank KOCH Richard A and BEIRNE Gilbert A The effect of treatment in latent syphilis Arch Dermat & Syph 69 91 1954

It has long been a question whether specific therapy was advantageous in latent syphilis Barnett first wrote philosophically on the subject (C W Barnett "Why treat latent syphilis?" Stanford M Bull 2 51 1944 "The effect of treatment on the prognosis of late latent syphilis" J Insur Med 4 7 1949 H L Blum and C W Barnett Prognosis in latent syphilis" Arch Int Med 82 393 1948) In the present paper however he and his group reported results of therapy in 2,470 patients treated with metal chemotherapy and 231 treated with penicillin Barnett introduced the novel idea of determining the effectiveness of treatment by the incidence of clinical progression per century of patient observation By this method of calculation it was shown that progression was less in those who received much treatment with metals than in those who received little Penicillin did not completely prevent progression

37 WILLCOX R R A WHO study of treatment schedules for early syphilis in use throughout the world Bull World Health Organ 10:579 1954

Section 19

MALARIA

Anemia	Ref 5
Avian malaria	Ref 13
Etiology	Refs 6 through 9 11 12 14 through 16
Exoerythrocytic cycle	Refs 46 50
Fertilization of parasite	Refs 23 through 35
Flagella	Refs 19 23 24 29
General	Refs 1 2 18 22 34 39 53
Immunity	Refs 32 52
Inoculation malaria	Refs 10 12 38
Melanemia	Refs 1 through 5
Modern chemotherapy	Refs 40 41 44 47 51 53
Mosquito	Refs 21 25 through 27 29 through 31 33 39
Parasite	Refs 7 through 9 11 12 14 16 20 48

(Continued on following page)

Section 19

MALARIA

THE present section like the one on tuberculosis has presented great difficulties the literature is overwhelmingly immense many items are relatively inaccessible in Italian journals and there are numerous offshoots into epidemiology preventive medicine protozoology and pharmacology As in previous chapters our guide has been the fact that this bibliography is compiled primarily for clinicians with general interests such as medical students and internists No apology is made therefore for slighting certain phases of the subject such as the public health aspects and some questions of immunity and of chemotherapy which the limits of space (and reason) make necessary No doubt many significant papers have been entirely overlooked

It should be recalled also that the two important decades 1880–1900—from the discovery of the parasite by Laveran to the culmination of Ross s work—was an era of bitter controversy of disputed claims of priority and even of accusations of frank plagiarism between the "Roman School" and first Laveran and later Ross In Ross s memoirs (Ref 39) there is even a chapter headed "Roman Brigandage" We have tried to deal fairly with this dispute although it is easy to see how Laveran and Ross felt themselves ill used

The striking clinical features of the intermittent fevers have given them an ancient and honorable medical history which has not been adequately dealt with by many writers We have not attempted therefore to go back of modern times that is to say earlier than the nineteenth century

For thorough discussions of every phase of the subject one should consult the monumental work on malariology" edited by Mark F Boyd (Philadelphia and London W B Saunders Co 1949) There are seventy chapters each by an authority in the field with comprehensive bibliographies Good reference lists to the older literature are to be found in Laveran (Ref 11) Marchiafava and Bignami (Ref 18) Mannaberg (Ref 20) Thayer and Hewetson (Ref 22) and Ross (Refs 36 39)

1 BAILLY E M Traité anatomico-pathologique des fièvres intermittentes Paris Gabon & Cie 1825

Reference is frequently made in the early literature to Bailly s book mainly because of the pathologic studies and he is often given credit for describing the characteristic malarial pigmentation of various organs Actually the text is long and discursive and the clinical pictures are too vague to have any useful meaning There are numerous case reports with gros autopsy findings These are not very satisfactory in the "pernicious" intermittent fevers arachnitis is a frequent diagnosis often with "splenitis" or "gastroenteritis The typical slaty or black pigmentation of the organs is mentioned only in passing no special significance was attributed to it and at best in an occasional case an organ was spoken of as dark (*foncé*) or grayish black (*gris-noiratre*) In summary the book serves best as a contrast for the advances in knowledge soon to come

Bailly was familiar with the use of quinine sulfate but thought of it as "a specific sedative for the abdominal nervous system" (p 426)

Pathology	Refs 1 2 4 48
Prevention	Refs 28 32 35 36
Quinine	Refs 2 43
Staining of parasites	Ref 17
Transmission	Refs 21 25 through 27 29 31 39

enlargement of the spleen of variable degree less so of the liver These and other organs often showed marked darkening sometimes they looked black The pigment was recognized as being related to the coloring matter of blood and there was more when the number of red cells was greatly diminished The association of acute comatose types of fever with plugging of the capillaries by innumerable "corpuscles filled with pigment was clearly recognized and the failure of quinine in some of these cases was thought to be explained by this Hemorrhages from plugged capillaries were described The exact relation of pigment to symptoms was not clear Cachexia with dropsy and skin pigmentation was occasionally noted Albumin and casts (Bright s disease) were observed in some cases Pigmented corpuscles were seen in the blood of *living* people—often ten to fifteen to a "field of the microscope" these were not thought to be red cells although the decrease in red cells was recognized

Where and how the pigment was formed were unknown there was no idea of a parasite and no understanding of phagocytosis by fixed tissue cells in organs Charcot insisted that the pigmentation was not a primary disease but he thought that the study of these phenomena "should perhaps one day form an important chapter in the general history of malarial intoxication"

One wonders why none of the many workers on the subject suspected the presence of parasites Poor microscopes lack of staining methods and study mainly of post mortem material may be the explanation

4 FRERICHS Friedrich Theodor von Klinik der Leberkrankheiten chap viii Veranderungen der Leber bei Intermittens p 325 Braunschweig F Vieweg & Sohn 1858

Frerichs the great German physician of the mid nineteenth century gave a detailed and authoritative description with beautiful plates of the pathology of malaria For Frerichs all the lesions were probably the consequence of the melanemia He described the pigment granules free in cells supposed to be leukocytes and in large cells probably of reticuloendothelial origin which he believed were lining cells of splenic sinuses Frerichs thought that in malaria as a result of febrile hyperemia the normal tendency of red blood cells to be destroyed in the spleen was greatly exaggerated with massive pigment formation from excess of hemoglobin (*blutroth*) liberation This in turn was carried to the liver and thence to other organs Why melanemia did not occur in other fevers with splenomegaly was a puzzle Frerichs descriptions were authoritative because they were based on autopsies made by him during the study of an epidemic of intermittent fever in Silesia in 1854–55

5 KELSCH A Contribution à l anatomie pathologique des palustres endemiques Arch de physiol norm et path **11** 2d ser 690 1875

Although the occurrence of anemia in malaria had long been known Kelsch seems to have been the first to make systematic blood counts during life He observed initial rapid declines often of as many as 1 000 000 cells a day with less rapid later changes He noted the extremely low counts in some cases of chronic paludism The old discussions of melanemia are again gone through but Kelsch did not get much further than Frerichs (Ref 4) Again there was no suggestion of parasites He thought that the pigment came from some obscure destruction of blood throughout the body not only or primarily in the

2 MAILLOT F G Traité des fievres etc Paris J B Bailliere 1836

Maillot s book eleven years after Baillys shows a good deal of advance The disease observed in France Corsica and Africa is now recognizable as malaria the clinical descriptions are excellent However there is as yet no precise dif ferentiation of tertian and quartan or of other types The deep pigmentation of organs is definitely noted in one case the liver was chocolate colored as was the spleen in seven cases (p 285) In five instances of the comatose type the brain had a blackish tint (p 287) However there was still no orderly synthesis of these observations and no realization that they had any special significance Quinine was used along with other febrifuges Maillot noted that where 5 grains of quinine sulfate were ineffective 20 grains might prevent further paroxysms

3 CHARCOT J M De la mélanémie altération du sang par des granules et des corpuscules de pigment Gaz hebd de méd 4 659 1857

Pigmentation of certain viscera especially spleen liver bone marrow and brain the mechanism of which is now clear was long ago widely noted as an empirical fact in connection with intermittent fevers We have already men tioned the observations of Bailly (Ref 1) and of Maillot (Ref 2) Richard Bright in his *Reports of Medical Cases* ([London Longman Rees Orne Brown & Green 1831] Vol 2, Case CI p 217 Pl XVII) pictured a section of a brain which was "almost the color of black lead Although this case is often quoted in the literature on malarial melanosis there is no satisfactory evidence for such a diagnosis

Meckel a psychiatrist is generally credited with being the first to note that brown pigmentation of organs in malaria was associated with an accumulation of pigment in the blood His case report (Heinrich Meckel "Ueber schwartzes Pigment in der Milz und dem Blute einer Geisteskranken *Allg Ztschr f* Psychiat 4 198 1847) is however difficult to interpret The patient had no clinical evidence of malaria and died in a psychotic state with weakness edema and ascites The brain was chocolate colored, the capillaries were full of pigment granules and the spleen was very large and dark brown Meckel thought the pigment was formed in the spleen whence it entered the blood He performed various chemical tests but did not identify the pigment Later ("Kornigen Farbstoff in der Milz und im Blute bei Wechselfieberkranken " Deutsche Klin 2 551 1850) he pursued the whole matter further and brought more evidence that certain kinds of pigmentation of blood and viscera are characteristic of malaria He now thought that the pigment came from blood which had been altered in the capillaries Virchow went a step further ("Zur pathologischen Physiologie des Bluts " Virchows Arch f path Anat 2 587 1849) in reporting an autopsy on a case of intermittent fever in which he described pigment in blood cells which he thought were leukocytes Whether or not any of these ob servers saw malarial parasites is hard to say at any rate they had no inkling of their nature

In Charcot s excellent article modern in tone is given an authoritative sum mary of current understanding of melanemia The following facts were accepted Melanemia (literally "black blood") of marked degree occurred only in asso ciation with intermittent fevers The pigment was brown or black in small or large clumps sometimes free in the blood or in organs but more often in cells or "corpuscles " which were regarded as leukocytes not as red cells There was

It is difficult to say who first saw the malarial parasite In systematic treatises various persons are mentioned whose descriptions of pigmented cells or bodies in the blood may have actually concerned the parasite but primitive micro scopes and inadequate technical methods without stains leave one quite un certain The bodies pictured by Virchow for example (Ref 3) bear no definite resemblance to the plasmodia

The actual discovery must be credited to Laveran The popular notion how ever that as he gazed into his microscope the parasites were immediately evi dent and the whole matter clear is far from the actual record Laveran s first communication was presented by proxy at the meeting of November 23 of the Academy of Medicine by M Léon Colin who stated that he had the honor to present for M le docteur Laveran stationed at the military hospital at Con stantine (Algiers) a manuscript entitled "Note on a new parasite found in the blood of several patients sick with malaria" The drawing which Laveran sub mitted is not reproduced but three types of elements are described in the blood "(1) These are elongated cylindrical slightly curved like a crescent showing in their center a spot made up of blackish granulations (2) other round bodies volume a little less than that of the red blood cells sometimes immobile sometimes moved by long tentacles which are attached to their bor ders (3) round elements much larger than the preceding, doubtless because of swelling of the cells by imbibition of serum

Colin went on to say in tactful terms that he doubted that these bodies were parasites partly because of the non-contagiousness of malaria and he proposed that a commission be set up to pass on the validity of similar future studies One can see that Laveran was to have a rough road

At the meeting of the academy of December 28 M Léon Colin again had a paper to present for M Laveran entitled "A second note relative to a new para site found in the blood of patients ill with malaria" ("Deuxieme note relative à un nouveau parasite trouvé dans le sang des malades atteints de la fièvre palustre" Bull Acad de méd 19 1346 1880) The communication consists however mainly of a blast by M Colin to the effect that Laveran s "parasites" were probably only leukocytes which had ingested pigment a phenomenon common in the melanemia of malaria Laveran evidently on the defensive now requested of the commission the aid of an expert histologist M Kiener of Val de Grâce which in civil life was Laveran s own university

8 LAVERAN A De la nature parasitaire des accidents de l impaludisme Compt rend Acad d sc **93** 627 1881

This time at the meeting of October 24 1881 of the Academy of Sciences Laveran spoke for himself "There are present in the blood of malaria patients parasites which present themselves under the following aspects He described four varieties (1) elongated crescentic bodies (2) spherical pigmented cells with filaments three or four times the diameter of a red cell in length (3) spher ical pigmented bodies of irregular form which however are not pigmented leukocytes (4) smaller spherical slightly pigmented bodies some only one sixth the diameter of a red cell 'The living nature of the spherical bodies in closing mobile grains of pigment and armed with mobile peripheral filaments is unquestionable" Laveran also noted pigment granules and pigmented white cells in the blood He stated that he had now studied nearly two hundred

spleen Even in the year when parasites were described (1880) the same absence of correct interpretation prevailed (Kelsch "Contribution a l'histoire des maladies palustres de la mélanémie" Arch gén de méd 146 385 1880)

6 KLEBS E and TOMMASI CRUDELI C Einige Satze uber die Ursachen der Wechselfieber und die Natur den Malaria Arch f exper Path u pharmakol 11 122 1879

The history of many infectious diseases such as scarlet fever influenza, poliomyelitis and others is that all sorts of bacteria were at first assigned a causal role As one was shown not to be the true agent another was blamed and this error might be repeated many times before the true etiology was established This was so with malaria the early literature on bacterial claims is reviewed by *Laveran (Ref 11 1891 pp 1 ff) and by Thayer (Ref 22 p 5)* However the findings of Klebs and Tommasi Crudeli supported by the authority of Klebs s name, seemed so plausible that they were generally accepted nearly twenty years later long after the discovery of the parasite an editorial article appeared in one of the leading English medical journals stating the causal role of the bacillus of Klebs as a settled fact (Thayer Ref 22 p 7)

Klebs and Tommasi Crudeli in brief claimed that they could extract from the earth of malarial regions and from the air near the ground bacteria which directly or in subculture when injected into rabbits produced a febrile illness with an intermittent type of fever resembling malaria enlarged spleen and at autopsy abundant black pigment in the spleen as in people ill with malaria They classed the organism as a bacillus and named it *Bacillus malariae*

Klebs seemed to have all the necessary controls and it is hard to understand how he could have erred so badly A few months later (E Klebs and C Tommasi Crudeli "Studien uber die Ursache des Wechselfiebers und uber die Natur der Malaria" Arch f exper Path u Pharmakol 11 311 1879) the earlier brief statement was elaborated into a tremendous article of eighty eight pages in which the details of the experiments leading to the same conclusions were given [1] It is of interest to note the large number of workers including such men as Marchiafava who thought that they had confirmed Klebs and Tommasi Crudeli Cuboni and Marchiafava for example began their paper on "New studies on the nature of malaria (Arch f exper Path u Pharmakol 13 265 1881) "Knowledge of the parasitic nature of malaria has received the most brilliant confirmation through the recent work of Klebs and Tommasi Crudeli"

7 [LAVERAN] Presentation by M Colin of a manuscript entitled Note sur un nouveau parasite trouvé dans le sang de plusiers malades atteints de fièvre palustre" Bull Acad de méd 9 1235 1880

[1] In 1924 I recorded in my diary an anecdote told me by Professor Kraus during a visit to Berlin "He [Kraus] began to speak of the malarial treatment of paresis and from this got on to malaria. It appears that before the discovery of the parasite Klebs joined an Italian commission and did some field work returning to Berlin with earth from the Roman Campagna From this he grew a bacillus about which there was great excitement and which was regarded as the possible causal agent Klebs inoculated two rabbits and left them overnight *with two assistants (one of whom I suspect was Kraus)* who were to watch and take their temperature The assistants got a jug of beer and played Skat and finally went to sleep and in the morning found the rabbits frozen to death Klebs then, in his lecture much excited said he couldn t demonstrate the temperature curves of the rabbits because they had died in the night *of malaria!*"

11 LAVERAN A Traité des fièvres palustres avec la description des microbes du paludisme Paris O Doin 1884

In 1881 after the appearance of his first paper (Ref 7) Laveran summarized the findings in a brief monograph entitled *Nature parasitaire des accidents de l'impaludisme Description d'un nouveau parasite trouvé dans le sang des malades atteints de fièvre palustre* (Paris O Doin 1881) He continued however to work energetically on the subject fighting a hard battle to convince others of the correctness of his views which were later embodied in his book of 1884 dealing with every phase of malarial fever In the Preface he stated that it was in studying the mode of formation of the well known pigmented elements in malarial blood that he was led to discover their parasitic nature He continued somewhat nostalgically "On November 6 1880 I demonstrated for the first time the presence of mobile filaments which adhered to the pigmented bodies and the living nature of which could not be in doubt At this very moment I had the intuition that I was in the presence of the true parasites of malaria and everything I have done since has confirmed this impression" No indication of this sudden and dramatic revelation is given in his original reports (Refs 7 8) This book went through many editions in the next thirty years Another important monograph appeared later (*Du paludisme et de son hématozoaire* [Paris G Masson 1891]) which was translated into English by J W Martin (*Paludism by Dr A Laveran* [London New Sydenham Society 1893]) There is an excellent historical introduction Although Richard (Ref 9) believed that the parasites were intracellular Laveran still felt that "our knowledge of the structure and composition of the blood-corpuscle in man makes it difficult for us to understand how these parasites can enter them The probability is that they simply adhere to the corpuscles by pressing upon them What makes this supposition more likely to be true is that the parasitic elements are often found in the blood in a free state" (p 16) The latter statement is of course erroneous Laveran recognized some difference between the parasites in various types of malaria decolorization of red cells in tertian in contrast to quartan diminution in size of parasitized red cells in quartan fever and differences in segmentation in tertian and quartan fever He was not certain that crescents were restricted to any special type of fever as others had claimed Although he quoted Golgi as believing that there are different races of malarial parasites in the excellent plate at the end of the book all types—segmenters flagellates and crescents—are mixed together Every phase of the disease including prophylaxis and therapy is discussed and there is a section on avian malaria

12 MARCHIAFAVA Ettore and CELLI Angelo Nuove ricerche sulla infezione malarica Arch per le sc med 9 311 1885 (A German translation of the manuscript was published simultaneously "Neuere Untersuchungen uber die Malariainfection" Fortschr d Med 3 39 1885)

Marchiafava s name has become so exalted in the history of malaria that it becomes important to analyze his work critically Marchiafava stubbornly supported the etiological role of Klebs and Tommasi Crudeli s malaria bacillus" long after Laveran reported his work (Refs 7 8) Marchiafava and Celli in 1882 denied the parasitic nature of Laveran s bodies although Laveran went to

patients with malaria Most of those who showed no parasites had been treated with quinine Parasites were found in no other disease He noted that the para sites were most likely to be found shortly before the paroxysm of fever but that in stubborn cases they were there all the time He thought that between bouts of fever the parasites resorted to internal organs especially liver and spleen He noted in autopsies on malignant cases how the internal capillaries were packed with pigmented bodies He concluded Attacks of malaria are produced by the introduction into the blood of parasites which appear in the various forms here with described it is because quinine kills these parasites that it cures malaria"

9 [RICHARD E] Sur la parasite de la malaria Compt rend Acad d sc 94 496 1882

Although Laveran s name now stands out one must picture the tremendous ferment of activity which went on in the study of malaria in the 1880 s For the most part doctors were skeptical or downright hostile to Laveran s claims There were those who adhered to a bacterial cause like the bacillus of Klebs (Ref 6) there were those who believed spores or molds were the etiological agent and many still held to bad air or swamp emanations and did not believe in a *contagium vivum* of any sort One can picture the patient hours spent at the microscope by faithful students as a "wild surmise" dawned that they might be looking at a living parasite One of the earliest supporters of Laveran was his friend Richard who worked in the hospital at Philippeville (Algeria) where there was much malaria Richard read this paper before the Academy of Sciences on February 20 1882 The same remarks were published in the Gazette médicale de Paris in the issue for May 20 1882 (4 252) Richard con firmed and strongly supported the discovery of the parasite which Laveran had named *Oscillaria malariae* because of the dancing appearance of the pigment granules He examined fresh blood unstained and emphasized the fact still true that this is the best way to study the motility of the parasite He differed with Laveran in one important point Laveran thought that the parasite was on the cell Richard was sure that it was in the red cell in which "it develops like a weevil in a lentil" He described the growth of the parasite at the cost of the host cell *until it was finally surrounded by a mere veil Filaments* were then thrust forth and finally the parasite burst from its shell

10 GERHARDT C *Ueber Intermittens Impfungen* Ztschr f klin med 7 372 1884

Inoculation malaria later to become an everyday procedure in the treatment of paresis *(Ref 38) seems to have been first attempted by Gerhardt* A hypoder mic syringe full of blood from the thirty seven year-old Brewer G with inter mittent fever was injected subcutaneously into the thirty nine year old hysteri cal B S on August 11 1882 On August 22 there were chill and fever and splenic enlargement The fever subsided after quinine Gerhardt later repeated the procedure in another case Nothing is said of parasites in this report and there were no bacteriologic studies After the parasite was recognized attempts at transmission by inoculation were soon made the early literature is well sum marized by Thayer and Hewetson (Ref 22 pp 35 ff) and very completely by Ross (Ref 36 pp 66 ff)

media In most cases the cultures remained sterile "In others one obtained cul ture products which were morphologically identical with the initial forms [of the parasite] The multiplication of these bodies was especially evident in slide cultures of malarial blood"

It is obvious then that Marchiafava and Celli were still unclear about the significance of their findings and in essence did little more than confirm La verans findings

A little later Marchiafava and Celli (Studi ulteriori sulla infezione malarica" Arch. per le sc med **10** 185 1886 German translation from the manuscript in Fortschr d Med. **3** 787 1885) elaborated their previous observations They emphasized the small non pigmented ameboid forms as their own discovery and followed them through to segmentation, which they thought was a method of multiplication to be followed by the invasion of the red cells by the liberated granules They insisted that pigment was a product of the transformation of hemoglobin It was in this paper that they suggested the name "plasmodium" or "hemoplasmodium" biologically unsound but later universally adopted [3] In this paper also the feud between Laveran and Marchiafava became overt We can not give the details of the controversy further but Laverans side is summarized in his book on *Paludism* (Paris G Masson 1891) pp 48 ff

13 DANILEWSKY B Zur Parasitologie des Blutes Biol Centralbl **5** 529 1885–86

Danilewsky under the heading of "The Hematozoa of Birds" enumerated three forms The description of the third form—clear rings which assume a spherical shape when more developed—could hardly have been anything else than "bird malaria" No analogy to the parasites of human malaria is suggested

Many varieties of malaria in birds were later described they have been of immense importance in the development of knowledge of the disease The epoch making observations of MacCallum on fertilization (Ref 24) and of Ross on the cycle in the mosquito (Ref 27) were made with bird malaria Finally during the second World War innumerable potential antimalarials were screened by means of their effect on malaria of ducks

14 COUNCILMAN W T and ABBOTT A C A contribution to the pathology of malarial fever Am J M Sc. **89** 416 1885

Although the prevalence of malaria in Italy and North Africa stimulated the early work of French and Italian observers interest was soon aroused in this country The foreign reports had hardly appeared before enthusiastic young American physicians began to study the subject in those regions of the eastern seaboard where malaria was prevalent However most of this work was done in a spirit of confirming or disproving those foreign observations which were the subject of active controversy Councilman and Abbott described in meticulous detail the lesions in two patients dead of "comatose malaria" They described the intense pigmentation of the organs and the small cerebral vessels choked with pigmented hyaline masses as if they were outlined in ink. The writers discussed the controversy as to a bacillary or protozoal cause and like many early

[3] For a full discussion of nomenclature see Sir Gordon Covell, P F Russell and N H Swellengrebel, *Malaria Terminology* ("Monograph Series" [Geneva World Health Organization 1953])

Rome and gave a demonstration of their presence in local cases[2] of malaria (Ref 11 1884 p viii and 1891, p 48) In 1883 Marchiafava and Celli ("Die Veranderung der rothen Blutscheiben bei Malariakranken" Fortschr d Med 1 573 1883) hedged Without any mention of Laveran they described what obviously were malarial parasites What now is the meaning of these bodies which we see [in malaria] within the red cells? Are they a regressive metamorphosis, or are they foreign elements which have entered the cells? At the present time we lean to the latter interpretation and presume that we are concerned with a parasite however none of this can be settled definitely as yet We hope to clear the matter up by further work, meanwhile the first mentioned possibility that we may be dealing only with a regressive metamorphosis of red cells is still to be considered" This is evasive to say the least Laveran further said (Ref 11 1891 p 48) In a letter dated Rome April 9 1884 M Marchiafava makes it clear that he and his collaborators have reached conclusions very different from mine "We believe that the pigmented forms which you [Laveran] have described are nothing but degenerated and pigmented red cells There can be no doubt on this point four years after the publication of my work they thought that the parasite of paludism was a micrococcus"

It would be interesting if one could reconstruct the medical politics of the time Klebs and Tommasi Crudeli were big names The latter was head of the bacteriologic institute in Rome Marchiafava worked in the same institution There must have been great pressure to take sides in this controversy with a relatively insignificant doctor from Val de Grâce

However by 1885 Marchiafava and Celli seem to have been suddenly committed to a parasitic cause for malaria Marchiafava had become an expert on stained smears and turning now to fresh preparations he laid special emphasis on small ring forms which might be ameboid and which contained no pigment He also described larger pigmented forms for the discovery of which as well as crescents he gave credit to Laveran In four among forty two cases carefully studied the flagella (*filaments mobiles*) also seen by Laveran were noted The activity of the flagella is vividly pictured Marchiafava and Celli pointed out that filaments were not seen in stained blood There is also a description of what seem to be segmenters and segmentation although the drawing of *scissione* ("division") is inaccurate and pictures a cell containing innumerable closely packed granules Flagella and crescents were seen much less often than the other cells but were constantly present in pernicious fever Marchiafava and Celli raised the question of whether segmenters gave rise to a new generation of parasites and begged the question about the significance of filaments other than that they were living bodies They felt certain that the small ameboid bodies were parasites which entered the red cells and destroyed them

They went on to describe attempts at transmission by injecting into a volunteer about 1 cc of blood freshly drawn from a malaria patient The fact that they produced "typical" malarial fever found the characteristic bodies in the blood and made them and the fever go away with quinine—"all these circumstances make our hypothesis that these are living forms probable"

Finally efforts were made to cultivate the parasite on ordinary bacteriologic

[2] Marchiafava and Celli described this visit and denied that Laveran had demonstrated the parasites (Arch ital biol 9 308 1888)

cerned the differences between quartan and tertian parasites are well described Golgi did not as yet positively assert that these were immutably different species

16 GOLGI Camillo Sul ciclo evolutivo dei parasiti malarici nella febbre terzana Arch per le sc med 13:173 1889 (German translation Ueber den Entwickelungskreislauf der Malaria Parasiten bei der Ferbris tertiana Fortschr d Med 7 81 1889)

By 1889 Golgi had clearly settled the fact that the various clinical forms of malaria were caused by distinct races of parasites The well known differences between the parasites of tertian and quartan fevers are systematically summarized He noted that the early forms of tertian were more motile than quartan and that there was less early pigment formation he observed the rapid decolorization of the red cells in tertian and the difference in number of segments in the two forms he saw that the quartan merozoites were larger than the tertian and that the quartan parasites had larger pigment granules He also described bodies which may well have been sexual forms In addition he said We now have reason to speak of still a third variety of malaria which is linked with the presence of the crescent like bodies of Laveran" He noted the resistance to quinine of these bodies and pointed out the "irregular development" of the younger forms in this sort of (estivo autumnal) malaria The article is a classic and must be read in detail

It is of interest that as late as 1891 Laveran denied the existence of several parasites and indeed of more than one form of malaria "In 1884 I reached the conclusion that the different forms under which the hematozoa of malaria present themselves belong to one and the same polymorphous parasite since then I have always defended this opinion" (Ref 11 1891 p 126)

The cycle of estivo-autumnal fever was worked out by Marchiafava and Celli whose preliminary report appeared in Riforma med 5 1281 1889 and by Canalis Riforma med 5 1443 1889 The proof of a separate species was given by other Italian investigators (Tito Gualdo and Enrico Antolisei "Inoculazione delle forme semilunari di Laveran" Riforma med 5 1640 1889) who gave a paretic person 2 cc of blood intravenously from a patient whose blood contained crescents The recipient developed malaria with crescents

An immense amount of further work on the details of the parasitic cycle in relation to clinical events was carried out in the next few years largely by the Italian school These papers are reviewed in detail by Thayer and Hewetson (Ref 22)

17 ROMANOWSKY D Zur Frage der Parasitologie und Therapie der Malaria St Petersburg med Wchnschr 15 297 307 1891

No sooner had the parasites been generally accepted as living bodies than many workers began to study the details of their structure The early work is reviewed by Thayer and Hewetson (Ref 22 p 45) Romanowsky in this paper described the staining methods which still bear his name and reported important histologic studies of the malarial parasite

An authoritative modern discussion is to be found in *Manual for the Microscopic Diagnosis of Malaria in Man* by Aimee Wilcox (National Institutes of Health Bull 180 [2d ed rev Washington D C Federal Security Agency

writers begged the question We confess our inability to say what these hyaline bodies are

In the same year Councilman (Certain elements found in the blood in cases of malarial fever Tr A Am Physicians 1 89 1886) presented a critical dis cussion of the whole subject at the Association of American Physicians "What the real nature of this body is—whether it is a parasite and the cause of malaria time and further investigation will show In the discussion Osler said "I am not prepared to give a positive opinion as to the nature of these bodies They look to me more like vacuoles or areas of hyaline transformation than defi nite organisms One year later Councilman had described and accepted the parasites as the cause of malaria and he clearly related different forms of the parasite to different clinical types of disease where the crescentic or elongated masses are found he has either some form of remittent [not intermittent] fever or malarial cachexia" ("Further observations on the blood in cases of malarial fever M News 50 59 1887)

Another early American student who did important work was Sternberg who reviewed the literature and described confirmatory observations of his own He was inclined to accept the parasites as the cause of malaria (George M Stern berg 'The malarial germ of Laveran " M Rec 29 489 517 1886)

Finally there should be mentioned the later studies of Osler (The haemato zoa of malaria " Brit M J 1 557 1887) who observed the parasites now related them to malaria and discussed their diagnostic value

Many other Americans at about this time contributed useful studies on ma laria but they made no fundamental advances All this work is reviewed by Laveran (Ref 11) and by Thayer (Ref 22)

15 GOLGI Camillo Sull infezione malarica Arch per le sc med 10 109 1886 abstract in German by Carl Gunther Fortschr d Med 4 575 1886

As everyone came to accept the parasitic cause of malaria it was natural to inquire whether the different forms of fever were caused by special types of plasmodia Laveran (Ref 11 1884 p 196) said that one could raise the question of whether in the intermittent fevers the nature of the parasitic ele ments varies with the type of fever He came however to no definite conclu sion Golgi took the first step toward distinguishing different types of parasites when he observed that in the quartan fevers prevalent in Pavia it took the whole length of the clinical cycle for the parasites which developed in orderly fashion to reach the segmented stage He also observed that segmentation preceded a paroxysm and that immediately thereafter the parasites seemed to disappear from the blood only to return as the cycle was renewed *He did not however in this paper positively claim that there was a special race of parasites in quartan fever* although his pictures show beautifully that the segmenters always consisted of less than twelve merozoites Golgi stated that the ameboid non pigmented forms were probably distinct from the pigmented forms al though in a later paper (Ref 16) he denied this

A little later Golgi ("Ancora sulla infezione malarica " Gazz d osp 7 419 1886, German abstract Fortschr d Med 4 692 1886) extended these metic ulous observations to tertian fevers The findings were analogous to those in quartan fever as far as an orderly development of the parasitic cycle is con

were concerned with reproduction From inoculation experiments in which the type of parasite in the injected blood was almost always found in the disease which was produced he concluded that each parasite is a true species which does not undergo a transformation into other forms there was a definite relation between the species of parasite and the type of fever He had no idea how the disease was transmitted and was puzzled by the varying length of the incubation period There are detailed descriptions of the parasites at all stages of the cycle and beautiful plates of both stained and fresh preparations

21 MANSON Patrick On the nature and significance of the crescentic and flagellated bodies in malarial blood Brit M J 2:1306 1894

The story of the association of the mosquito with malaria is of great interest One wonders over and over again how the causal relation could have been missed in view of the close association of mosquitoes with the circumstances of the disease

King in a much-quoted paper (A F A King, "Insects and disease—mosquitoes and malaria" Pop Sc Month 33 644 1883) without any reference to the parasite gave an orderly argument in favor of the mosquito as the transmitting agent This is based on analogy to other mosquito-transmitted diseases—filariasis and perhaps yellow fever—and on the association of mosquitoes with malaria King of course did not know just how such transmission was brought about Laveran (Ref 11 1891 p 147) remarked that "perhaps these insects [mosquitoes] play a role in the propagation of malaria as they do in filariasis" but he pursued the idea no further Similarly others had mentioned more or less casually the possibility of insect transmission but no one seemed inclined to perform any purposeful experiments until Manson There is a good review of the early literature in Nuttall s monograph (Ref 30 pp 75 ff)

Manson s paper seems to be the first in which any really impressive claim was made Manson described and emphasized the forms later known to be gametocytes described exflagellation and reasoned clearly that the crescents and analogous spherical forms as well as flagella must have something to do with the propagation of the malarial process outside the human body As there was no evidence that the parasites left the body in the excreta or through the skin since the disease could be transmitted by injection of blood from malaria patients and since filariasis a disease in many ways analogous to malaria had been proved to be transmitted by the mosquito Manson concluded that malaria also must be transmitted either by the mosquito or by some other suctorial insect He postulated a cycle in the mosquito but thought that it was not worth speculating further when experimental work could easily be done this he hoped someone would achieve in the proper area such as India Manson s argument clearly included the flagella as an active and essential part of the cycle produced only outside the human host, and not as a degenerative stage of the parasite as the Italian school held (Ref 18) Manson did not know what happened in the mosquito or how the parasite returned to man he did not state that it must be by mosquito bite but at first rather thought it was by way of ingestion of water contaminated by infected mosquito larvae

22 THAYER William Sidney and HEWETSON John The malarial fevers of Baltimore Johns Hopkins Hosp Rep 5 3 1895

Public Health Service, 1950]) Both technical matters such as the preparation of films and the finer microscopic appearances of various forms of parasite are described.

18 MARCHIAFAVA, E and BIGNAMI, A Sulla febbre malariche estivo-autumnali Roma E Loescher 1892 (English translation by J Harry Thompson [London New Sydenham Society 1894])

Following the original work of Marchiafava and Celli (Ref 12) there was an immense resurgence of malarial study by the "young Roman" group of physicians To be mentioned are Celli Bignami Bastianelli Grassi Feletti and others We cannot list the numerous papers but their work dealt with the significance of the various parasitic bodies the life cycle of the parasites their relation to the course of the disease the effects of quinine upon them and clinical classification and description of the various fevers in relation to the type of parasite involved

Most of this work was summarized in this important book of Marchiafava and Bignami They clearly described the different species of parasites and emphasized the spherical forms as the important part of the cycle whereas Laveran had stressed the mobile filaments as the completed parasite They perceived the relation between liberation of the spores by segmentation and the paroxysm related the crescents to estivo autumnal fever but thought that they were degenerated forms of the parasite studied in detail the relation of quinine to inhibition of the parasite at various stages of the cycle, described accurately the malignant and comatose forms and related them to plugging of the cerebral vessels by parasite containing red cells They had no idea of the sexual cycle and no inkling of the real meaning of crescents and flagella There are excellent illustrations of parasites This book is a storehouse of knowledge of the whole subject to date

19 SAKHAROFF N Recherches sur les hématozoaires des oiseaux Ann Inst Pasteur 7 801, 1893

There had been great dispute as to the significance of the flagella of malarial parasites Some especially the Italian school thought of them as degenerative dying forms to others they seemed to be active bodies which must fulfil some important purpose Sakharoff noted that the flagella of "crow malaria" contained nuclear material "In our opinion the exit of chromatic filaments from the parasite and their energetic movements in their free state in the blood plasma are facts which could be of general significance in cellular biology

This was soon to be verified by the observations of Simond (Ref 23) and of MacCallum (Ref 24) and elaborated many years later by MacDougall (Ref 49)

20 MANNABERG Julius Die Malaria Parasiten Vienna A Holder 1893 (English translation by R W Felkin [London New Sydenham Society 1894])

This scholarly book gives an authoritative summary to date of the knowledge of the malarial parasite based on Mannaberg's own work and on a comprehensive review of the literature Mannaberg pointed out the widely differing views on crescents and on the basis of morphology thought it likely that they

25 ROSS Ronald Observations on a condition necessary to the transformation of the malaria crescent Brit M J 1:251 1897

Ross threw himself into the controversy between Manson and Bignami (Amico Bignami "Le Ipotesi sulla biologia dei parasiti malarici fuori dell uomo" Policlinico 3 320 1896) on the significance of crescents and of exflagellation The Italian school as we have said looked on this as a degenerative involutional process in other words the flagellum was a dying form Manson on the other hand thought that the crescents and flagella represented a vital stage in an extra-corporeal cycle of the parasite Exflagellation presumably did not occur in human circulating blood but only after the blood had been altered in some fashion Ross showed that if mosquitoes fed on a patient whose blood contained many crescents there was a rapid change within the insect from crescent to sphere to exflagellation In this paper he went no further in elucidating the cycle in the mosquito

26 ROSS Ronald On some peculiar pigmented cells found in two mosquitos fed on malarial blood Brit M J 2 1786 1897

In this paper Ross went a step further In mosquitoes fed on patients whose blood contained many crescents he later found peculiar pigmented cells which suggested the presence of a parasitic stage The specimens were sent to authorities in England no one was certain but Manson wrote "Considering the peculiar groupings of the pigment in many instances a grouping that forcibly recalls what one sees in the living malaria parasite and the distinctness and regularity of the outlines of the bodies I am inclined to think that Ross may have found the extra-corporeal phase of malaria "[6]

27 [ROSS] The role of the mosquito in the evolution of the malarial parasite the recent researches of Surgeon Major Ronald Ross I M S Lancet, 2 488 1898

---

meeting of the Johns Hopkins Hospital Medical Society on November 16 1896 and their preliminary findings were published in the Johns Hopkins Hospital Bulletin (8 51 1897) Neither then nor later however did they publish jointly and Opie to all intents seems to have disclaimed the fertilization idea when he wrote "After a while individual flagella not infrequently become detached and float away continuing their active serpentine movements After persisting for some time the flagella become less active and finally disappear by exactly what process can not be said in every case" (On the haemocytozoa of birds " J Exper Med 3 95 1898) Can it be that these brilliant medical students disagreed and that Opie did not accept at least at the time MacCallum s observation?

[6] In reading textbook accounts of these transactions (for example P F Russell L S West and R O Manwell *Practical Malariology* [Philadelphia W B Saunders Co 1946] p 11) one gets the impression that Ross suddenly saw a parasite developing in the mosquito and that he "had no doubt that he was looking at the malaria parasite " Nothing could be more misleading Ross s ideas evolved gradually and painfully in the course of immense labor It would of course be absurd to attempt final conclusions as yet," "they seem to open the question of their being indeed the form of haemamoeba we are in search of " the parasitic nature of the cells cannot finally be accepted until certain facts as to structure sporulation and so on have been demonstrated are phrases which Ross used in his paper The whole story is vividly told in Ross s memoirs (Ref 39 pp 225 ff)

This monograph is the first comprehensive and authoritative American work on malaria [4] There is a thorough review of the literature with a bibliography of 359 references dealing with all the early experimental work The authors own meticulous clinical and parasitological observations are next presented and finally the classical drawings of malarial parasites by Max Broedel are here reproduced for the first time Supplementary to this report is Thayer s *Lectures on the Malarial Fevers* (New York D Appleton & Co 1897) These works are definitive to date and still make exciting and valuable reading

23 SIMOND P L L Evolution des sporozoaires du genre Coccidium Ann Inst Pasteur 11 545 1897

Simond working with *Coccidium oviforme* concluded that the flagellate bodies are male sexual forms He did not actually observe conjugation but paved the way for MacCallum s work (Ref 24) The mobile stage of *Coccidium* gives the most rational explanation of the flagella of malaria we should recognize the possibility of conjugation necessary for the production of a resistant form"

24 MacCALLUM W G On the flagellated form of the malarial parasite Lancet 2 1240 1897

In this brief paper MacCallum working with the malaria of crows (Halteridium), vividly described the formation of flagella and their conjugation with other sexual forms "The granular forms lie quiet beside the nuclei and shadows of the red blood corpuscles which lately contained them but are soon seen to be approached by the flagella which having torn themselves away from the hyaline organism from whose protoplasm they were formed struggle about among the corpuscles—one of them plunges its head into the sphere and finally wriggles its whole body into that organism" This epoch making observation was confirmed in the case of a woman with estivo-autumnal fever and finally resolved the numerous erroneous speculations of previous observers as to the significance of flagellated forms

This paper was preceded by a brief note in the Johns Hopkins Hospital Bulletin describing conjugation (On the haematozoan infection of birds" 8 235 1897) in which MacCallum gave Opie credit for describing the hyaline and granular sexual forms and for suggesting that the hyaline bodies gave rise to flagella (see E L Opie "On the haemocytozoa of birds J Exper Med 3 79 1898) In a later paper (On the haematozoan infections of birds J Exper Med 3 117 1898) MacCallum described the process of flagella formation and conjugation in much more detail with a good drawing of the process He had no idea however of the subsequent fate of the fertilized cell and made no mention of the mosquito An analysis of previous views of the significance of flagellation is a useful part of this paper [5]

[4] The book by George M Sternberg *Malaria and Malarial Diseases* (New York W Wood & Co 1884) is definitely premodern in tone and there is no mention of the parasite which Laveran had described four years previously

[5] It is of interest that in historical accounts and in bibliographies (*see* for example F H Garrison and L T Morton *Medical Bibliography* [London Grafton & Co 1943] pp 267-68) the name of E L Opie is often coupled with that of W G MacCallum in this discovery Both were medical students working at the same time on avian malaria under the supervision of W S Thayer Both presented their observations at the same

ventive and other public health measures in malaria The brilliant work of Ross in Sierra Leone the triumphs of Gorgas in Havana and in the Canal Zone the useful efforts in the South Pacific in World War II require an extensive bibliography of their own (but see Ref 36)

29 MANSON Patrick Experimental proof of the mosquito-malaria theory Brit. M J 2 949 1900

It is hard now to appreciate the general resistance in 1900 to belief in the mosquito theory of malaria transmission Although A Bignami ("The inoculation theory of malarial infection" Lancet, 2 1461 1541 1898) claimed in 1898 to have transmitted human malaria in Italy by mosquito bite many people were unconvinced In Manson s classical demonstration infected mosquitoes were sent from Rome to London and there allowed on August 29 to bite a volunteer (Manson s son) who developed typical malaria on September 13 with tertian parasites in the blood and who was cured by quinine[7] Conversely Drs Sanborn and Low and Signor Terzi set up a mosquito-proof hut in an intensely malarial spot in Italy and lived in it from July to September without acquiring malaria "in marked contrast to their neighbors who were all of them either ill with fever or had suffered malarial attacks" Manson drew important conclusions from these experiments as to malaria control and prevention

30 NUTTALL, George H F On the role of insects arachnids and myriapods as carriers in the spread of bacterial and parasitic diseases of man and animals a critical and historical study Johns Hopkins Hosp Rep 8 1 1900

This is a valuable review of parasites in relation to disease including malaria with useful bibliography of early work on mosquitoes and mosquito control

31 GRASSI Battista Studi di uno zoologa sulla malaria Rome Tipografia della R Accademia dei Lincei 1900 also 2d ed. 1901

This classical monograph handsomely printed with beautiful color plates deals with the work to date of the "Roman school" on every phase of malaria in relation to mosquitoes The book has been bitterly attacked by Ross (Ref 39) and others on the grounds of plagiarism The Italians certainly took advantage of the fact that Ross had not had the opportunity to follow the cycle of *human* strains of malarial parasites in the mosquito to belittle his work[8] However we must let the individual reader adjudicate this dispute[9] and, at any rate the book is a storehouse of valuable information on mosquito transmission

32 KOCH R Zusammenfassende Darstellung der Ergebnisse der Malaria Expedition Deutsche med Wchnschr 26 781 801 1900

[7] This story is vividly retold in Ross s memoirs (Ref 39 p 417) and there is a complete summary of all the early mosquito inoculations in Ross, Ref 36 pp 77 ff

[8] A note in the British Medical Journal (2 608 1899) entitled "The cultivation of the malarial quartan parasite in Anopheles" is a report of a telegram from Ross in Africa stating that he had studied the quartan cycle in the mosquito

[9] For a fair appraisal of the claims of Ross and of the Italian school see George H F Nuttall On the question of priority with regard to certain discoveries upon the etiology of malarial diseases" Quart. J Micr Sc., 44 Part I, 429 1900.

At the meeting of the British Medical Association Manson reported the latest news of Ross's investigations on bird malaria (*Proteosoma*) in India Ross had found that the pigmented bodies (Ref 26) progress to "coccidia" which penetrate the stomach of the mosquito and protrude into the celom "The coccidia now burst and germinal vermicules which had been formed in its interior are set free in the body, blood and tissues of the mosquito Then came the discovery of those vermicules in the veneno-salivary glands of the mosquito" Finally, Ross allowed mosquitoes to feed on infected birds and a few days later permitted these insects to bite birds whose blood was "void of any parasite infection The birds became infected and their blood was charged with parasites "Thus the analogy between bird and human infection has only to be proved to establish that the mosquito is a carrier of malaria and an infector of man The modest wording does not convey the full import of Ross's epochal clarification of the malarial cycle in the mosquito and the proof that the parasite was conveyed to man by bite and not by infected water

This report was amplified a little later by a communication by Ross to the British Medical Journal (Mosquitos and malaria 1 432 1899) for Ross's other numerous communications on his discoveries the reader is referred to the bibliography given in his memoirs (Ref 39)

While Ross is clearly responsible for tracing the cycle in the mosquito from gametocyte through to the salivary gland he did not himself observe fertilization in the stomach blood of the mosquito as Schaudinn did later (Ref 35), and he did not have an opportunity personally to produce malaria in volunteers with human strains as Manson did (Ref 29) or to study the cycle of a human parasite in the mosquito until 1899 (Ref 31)

28 ROSS Ronald The possibility of extirpating malaria from certain locations by a new method, Brit M J 2 1 1899

Laveran as early as 1891 (Ref 11 p 147) remarked "Mosquitoes always abound in malarial regions and one notes that soil drainage which suppressed the fevers also suppresses the mosquitoes Perhaps these insects play a part in the propagation of malaria as they do in filariasis" He pursued the matter no further at the time

But no sooner had the spread of malaria by the mosquito been proved than men of wide vision began to think about mass preventive measures It is almost unbelievable how resistant physicians in general were to these ideas as well as the bureaucrats without whose support nothing could be done Ross a pioneer in malaria control told vividly about these difficulties in his memoirs (Ref 39) In the present paper he discussed measures for eliminating the types of mosquito which carry malaria by draining and otherwise getting rid of the fresh water pools in which they bred This method of malaria prevention–mosquito control–has of course been of immense importance in the subsequent history of the subject Koch on the other hand (Ref 32) was doubtful about the feasibility of eliminating mosquitoes but on the basis of his work in Africa proposed giving quinine to everyone infected with malaria especially in the chronic cases with no fever to prevent the mosquitoes from ingesting parasites Manson (Ref 29) laid emphasis on screening

It is impossible in this bibliography to list all the important work on pre-

period of probation has been completed and the time for action has arrived Nothing will stimulate public action in this matter so much as will the authoritative support of our principal men of science"

35 SCHAUDINN Fritz Studien uber Krankheitserregende Protozoen II Plasmodium vivax (Grassi und Feletti) der Erreger des Tertianfiebers beim Menschen Arb a d k Gsndhtsamte 19 169 1903

In this thorough monograph on the life-cycle of the tertian parasite Schaudinn gave a minute and vivid description of fertilization in blood withdrawn from the stomach of mosquitoes who had fed on a patient with clinical malaria thus *amplifying the work of MacCallum (Ref 24) and of Ross (Ref 25)* There are plates illustrating graphically the various stages of the process

In this communication Schaudinn also described sporozoites (from mosquito bite) actively penetrating and invading the red cells This work has never been confirmed but belief in Schaudinn s observations held back for many years work on the exo-erythrocytic cycle (Refs 46 50)

36 ROSS Ronald The prevention of malaria London John Murray 1910

This is a comprehensive discussion of every phase of malaria prevention definitive to date There are contributions by a number of authorities in addition to Ross A recent authoritative summary is that of Sir Gordon Covell "Current research toward a global control of malaria New England J Med **219** 125 1953

37 BASS C C and JOHNS Foster M The cultivation of malaria plasmodia (Plasmodium vivax and Plasmodium falciparum) in vitro J Exper Med **16** 567 1912

From the time of the discovery of the parasite attempts at cultivation have been made These early efforts in spite of some claims of success were all clearly failures A number of interesting experiments were however made on survival of the parasites in leeches which had fed on malarial patients O Rosenbach (Die Conservierung lebender Malariaparasiten " Berl klin Wchnschr 28 839 1891) believed that such parasites remained alive at least 48 hours N Sacharoff (Ueber den Einfluss der Kalte auf die Lebensfahigkeit der Malariaparasiten " Centralbl f Bakt 15 158 1894) found parasites still motile in leeches which had fed 7 days before Thayer and his associates confirmed these findings (Ref 22 *Lectures* p 27)

Bass in 1911 had made a preliminary note ("A new conception of immunity" J A M A 57 1534 1911) on his cultivation work but this is the definitive report The technique is given in full In successive cultures the asexual parasites grow segment and form rosettes which burst and give rise to merozoites many of which enter new red blood cells in exactly the same manner as they do in the body of man" It was important that *Plasmodium vivax* and *P falciparum* cultivated in identical fashion remained distinct The subject was carried further and its difficulties and complexities were discussed by W Trager (Studies on conditions affecting the survival in vitro of a malarial parasite [*Plasmodium lophurae*]" J Exper Med 74 441 1941 and Studies on the extracellular cultivation of an intracellular parasite [avian malaria]" *ibid* 92 349 1950) Geiman and his associates (Q M Geiman C B Anfinsen R W McKee R A

Koch working in New Guinea was one of the first to emphasize splenomegaly as an index of the degree of malarial infection in a locality He found it most common in children three to six years old who had had no evidence of active malaria for 2–3 years By the time these children were fourteen to fifteen years old the splenic tumor was no longer palpable other evidence of malaria had also disappeared Koch thought all this due to an immunity reaction Ross (Ref 36 p 127) discussed the matter systematically and introduced the term average spleen index " This has turned out to be very important from the epidemiologic and immunologic standpoints

33 GILES George M Handbook of the gnats or mosquitos London J Bale Sons & Danielsson 1900 also 2d ed, rewritten and enlarged 1902

During the whole of Ross s work on transmission, the definition of the varieties of mosquito which were carriers of malaria presented one of the great difficulties Mosquito classification in various areas was still inadequate and Ross did not at first speak of *Anopheles* or *Culex* but described the insects as gray or brown dapple winged and so forth It was the gradual evolution of the work of many students which led to the conclusion that only certain strains of *Anopheles* were capable of transmitting malaria

Giles s elaborate book was one of the early treatises in which mosquitoes were systematically described and those which transmitted malaria were identified During the whole history of malaria studies it has been necessary to appraise the type of mosquito at fault in various regions where the disease was encountered A key to the mosquitoes of the Australasian region was issued early in World War II (K L Knight, R M Bohart and G E Bohart [Washington National Research Council Division of Medical Sciences 1944] issued by the Office of Medical Information) A list of malaria transmitting anophelines is given in C F Craig and E C Faust *Clinical Parasitology* (4th ed Philadelphia Lea & Febiger 1945) p 642 in P F Russell L S West and R O Manwell *Practical Malariology* (Philadelphia W B Saunders Co 1946) p 587 and in T T Mackie G W Hunter and C B Watt *A Manual of Tropical Medicine* (2d ed Philadelphia W B Saunders Co 1954) p 294

34 ROSS Ronald Malarial fever its cause prevention and treatment London Longmans Green & Co 1902

Although most of the principal facts about malaria were known by 1900 people in general were reluctant to accept the mosquito theory of transmission and its epidemiologic implications

This little book by Ross is a classic In simple terms all the fundamental knowledge about the disease ("containing full details for the use of travellers sportsmen soldiers and residents in malarious places") is set forth with special emphasis on the public health aspects proper methods of using quinine and so forth But there is no longer any reason at all why we should suppose that the infection of malaria rises from water or soil *It is not the germ which rises from stagnant water it is the carrier of the germ which does so*" (author s italics) The book did a great deal toward education of the public about malaria

As early as 1900 Ross (J Soc Arts 49 17 1900) read a vigorous paper on malaria and mosquitoes It concludes with a strenuous plea for the government to apply the obvious preventive measures for malaria "In my opinion the

1926 Beih 3) At that time the importance of differentiating the action on the erythrocytic and on the exoerythrocytic stages of the parasite was not well understood and as the suppressive and preventive actions of the drug were not outstandingly better than quinine and there were important toxic symptoms its use was not pushed Sinton and Bird first clearly demonstrated the action of plasmochin in preventing relapses that is in producing radical cure Sinton J Smith and D Pottinger continued these studies ("Studies in malaria with special reference to treatment XII Further researches into the treatment of chronic benign tertian malaria with plasmoquine and quinine" Indian J M Research 17:793 1930) and showed that in situations where the relapse rate was 70 per cent or more in patients treated with quinine only the addition of plasmochin reduced the relapses to 30 per cent or less Other reports to the same general effect were those of S James W Nicol and P Shute ("The prevention of malaria with plasmochine" Lancet 2 341 1931) of H Most C Kane P Lavietes I London E Schroeder and J Hayman ("Combined quinine plasmochin treatment of vivax malaria effect on relapse rate" Am J M Sc 212 550 1946) working with Pacific strains of vivax and of R Berliner D Earle J Taggart W Welch C Zubrod P Knowlton J Atchley and J Shannon ("Studies on the chemotherapy of human malarias VII The antimalarial activity of pamaquine" J Clin Investigation 27 Part 2 108 1948) with experimentally induced *vivax* and *falciparum* malaria Here again pamaquine had a relatively feeble suppressive effect even in maximal doses If the schizogenous cycle was interrupted by quinine then the curative (anti relapse) effect was evident in *vivax* malaria

41 MAUSS H and MIETSCH F Atebrin ein neues Heilmittel gegen Malaria Klin Wchnschr 12:1276 1933

The writers discuss the composition and properties of Atabrine (quinacrine U S P) which was soon recognized as a valuable antimalarial Early trials (F M Peter "Ueber die Wirkung des Atebrin gegen naturliche Malariainfection Deutsche med Wchnschr 58 533 1932 L E Napier and B M Das Gupta "Atebrin synthetic drug for treatment of malaria" Indian M Gaz 67 181 1932 R Green "Report on 50 cases of malaria treated with Atebrin" Lancet 1 826 1932) did not fully answer the question of whether Atabrine was fundamentally superior to quinine although it has recently been claimed that Atabrine gives more prompt and effective control of parasitemia and symptoms and promotes longer intervals until relapse (Harry Most and Joseph M Hayman Jr "Relative efficiency of quinacrine [Atabrine] and quinine in treatment of acute attacks of vivax malaria Am J M Sc 211 320 1946) A shortage of quinine during World War II led to renewed study of Atabrine It was shown that its chemotherapeutic activity was a simple function of the plasma concentration ("Plasma quinacrine concentration as a function of dosage and environment a joint report of the Armored Medical Research Laboratory Fort Knox Kentucky and the Commission on Tropical Diseases Army Epidemiological Board Preventive Medicine Service Office of the Surgeon General United States Army Arch Int Med 78 64 1946) This work led to more intelligent dosage schedules for suppression and therapy of acute attacks The failure to prevent relapses (radical cure) the development of more effective

Ormsbee and E G Ball, "Studies on malarial parasites VII Methods and techniques for cultivation" J Exper Med 84 583, 1946) also have a valuable paper on the problem of cultivation F Hawking reviewed attempts to grow malarial plasmodia in tissue culture ("Tissue culture of plasmodia" Brit M Bull, 8 16 1951) The upshot of all this work is that as yet, there is no simple reliable method of cultivating human malarial parasites through successive generations

38 WAGNER JAUREGG Die Behandlung der progressiven Paralyse und Tabes, Wien med. Wchnschr 71 1106 1210 1921

The early inoculation experiments (Refs 10 12) were carried out purely to determine the transmissibility of malaria Wagner Jauregg however introduced inoculation malaria as a means of causing therapeutic fever in general paresis While the subsequent huge literature (authoritatively reviewed by J E Moore *The Modern Treatment of Syphilis* [2d ed Springfield Ill Charles C Thomas 1941] pp 374 ff) deals largely with the results of treatment valuable data have also been accumulated on the natural history of inoculation malaria (for example Warrington Yorke and J W S McFie "Observations on malaria made during treatment of general paresis Tr Roy Soc Trop Med & Hyg 18 13 1924) and its value in the study of immunologic questions and as a means of testing therapeutic agents has been widely explored N Kopeloff ("Inoculation malaria sexual and asexual strains Am J M Sc 197 800 1930) for example noted that after 7 months of transfer through patients a strain began to lose its capacity to produce gametocytes and became asexual A condensation of Wagner Jauregg s article soon appeared in English ("The treatment of general paresis by inoculation of malaria" J Nerv & Ment Dis, 55 369 1922)

39 ROSS Ronald Memoirs with a full account of the great malaria problem and its solution London John Murray 1923

In the course of these fascinating memoirs Ross tells the intimate story of his malaria research During the years in which this work was done (ca 1895-1900) Ross was a bitter disappointed man He had to work under the most adverse conditions he was frustrated over and over again by an incredibly stupid bureaucracy and when the discovery was finally made presumably reputable scientists tried to steal his glory and a skeptical public was inert to the tremendous sanitary implications Ross was essentially an idealist and a humanitarian His discovery thrilled him not as a biologist but because it indicated the way to elimination of a dread disease As he pointed out he was a sanitarian rather than a zoologist The book is a mine of source material and should be read by everyone interested in malaria or public health

40 SINTON J A and BIRD W Studies on malaria with special reference to treatment plasmoquine in the treatment of malaria Indian J M Research 16 159 1928

Plasmochin (pamaquine) a synthetic quinoline derivative had been described as an antimalarial drug in 1926 by Schulemann and others (Werner Schulemann and Guglielmo Memmi "Plasmochin ein Synthetisches gegen die Malaria infection wirksames Chinolin Derivat" Arch Schiffs u Tropen Hyg 30 59

effect The shortage of the supplv of quinine due to enemy action and the realization that neither quinine nor Atabrine was effective in completely eradicating the disease and preventing relapses led to a frantic search for new antimalarials and thousands of prospective compounds were developed and tested Out of this work came the new drugs which are effective in both suppression and eradication An idea of the "antimalarial drugs" situation in 1944 is obtained from this monograph intended to give the general background of present knowledge of the treatment of malaria by drugs under existing war conditions "

It should be emphasized that the few references on chemotherapy which we are able to include in this bibliography give no idea of the thousands of papers dealing with the effects of antimalarials Authoritative reviews to date are that of J A Shannon "Study of antimalarials and antimalarial activity in human malarias" Harvey Lect 41:43 1945–46 and that of N Hamilton Fairley Malaria Lecture II Chemotherapy" Brit M J 2 891 1949

45 ASH J E and SPITZ, Sophie Pathology of tropical diseases an atlas "Malaria" p 206 Philadelphia and London W B Saunders Co 1945

This is an authoritative account with beautiful plates of the pathology of malaria For a full description of the microscopic anatomy with extensive bibliography consult William H Taliaferro and H W Mulligan *The Histopathology of Malaria with Special Reference to the Function and Origin of the Macrophages in Defence* (Indian M Research Memoirs " [Calcutta 1933])

46 FAIRLEY N Hamilton Chemotherapeutic suppression and prophylaxis in malaria Tr Roy Soc Trop Med & Hyg 38 311 1945

The idea of an exo erythrocytic phase in human malaria was "in the air" in the 1940s and Fairleys work brought strong indirect evidence The failure of such drugs as quinine which eliminate trophozoite transmitted (inoculation) malaria to prevent relapses and produce permanent cure suggests that quinine resistant forms must be elsewhere in the tissues than in the blood Fairley also showed by subinoculation experiments that *vivax* sporozoites injected by mosquito bite disappeared from the blood to reappear 9 days later he presumed that they were developing outside the circulation Further elaborate and most instructive observations by Fairley and his associates on the results of subinoculations and the effect of drugs under various conditions ("Researches on Paludrine [M 4888] in malaria *ibid* 40 105 1946 and Sidelights on malaria in man obtained by subinoculation experiments" *ibid* p 621 1947) were made in the next few years but it remained for Shortt and Garnham (Ref 50) actually to demonstrate the pre erythrocytic tissue stage in man

Fairley also presumed that in contrast to *vivax P falciparum* has only a short lived tissue stage there is a brief pre erythrocytic stage but no subsequent exo-erythrocytic stage Radical cure can therefore be achieved by drugs such as quinine Atabrine and chloroquine which have only a suppressive effect in *vivax* malaria Fairleys important summary of the whole problem should also be consulted (Ref 52)

The early views on relapses are discussed in Rosss book (Ref 36 p 108) Some of these theories were that relapse was due to inadequate quinine therapy or temporary "encystment" of parasites in internal organs whence they "broke

drugs and the occurrence of severe toxic symptoms have led to its displacement The violent skin reactions are described in a series of articles in the Bulletin of the U S Army Medical Department (4 653 687 724 725 1925)

42 EATON Paul Susceptibility of red cells to malaria Am J Trop Med 14 431 1934

The question has often been raised of why malarial parasites do not multiply until every blood cell is infected Eaton offered an explanation of this in a case of inoculation malaria (presumably tertian) when he found that the parasite seemed only to invade the reticulocytes (young cells) He presumed that schizonts which do not infect are promptly phagocytosed This work was amplified by R Hegner ("Relative frequency of ring stage plasmodia in reticulocytes and mature erythrocytes in man and monkeys" Am J Hyg 27 690 1938) who found that tertian parasites mostly invaded young cells but that quartan and *falciparum* parasites were found mainly in mature red cells The exact meaning of all this work is not clear It is of interest that R Craick ("The erythrocyte in malaria Lancet 1 1110 1920) had found that stippled red cells resulting from ingestion of lead were prone to invasion by *P vivax*

43 HAGGIS A W Fundamental errors in the early history of cinchona Bull Hist Med 10 417 1941

For some three hundred years until the development of quinacrine cinchona bark or its alkaloids were the only effective therapy for malaria history owes quinine an unrepayable debt even though in the last ten years it has been largely replaced by more effective drugs (Refs 40 47 51 53) Haggis in an important study seems to disprove the traditional view that the Countess of Chinchon introduced the remedy into Spain when she returned with her husband from Peru The full history of the terms "cinchona and "quina-quina" is discussed

At the date when this bibliography begins the use of Peruvian bark in intermittent fever was common knowledge The subsequent literature is vast The quinine alkaloids were extracted by Pelletier and Caventou in 1820 ("Recherches chimiques sur les quinquinas Ann chim et phys 15 289 1820) and have been generally used since then Considerations of the action of quinine important to the clinician are reviewed by Laveran (Ref 11 1891 p 183) by Thayer and Hewetson (Ref 22) and by Ross (Ref 36) and a more modern summary is that of Erwin E Nelson Cinchona and its alkaloids in the treatment of malaria" in *A Symposium on Human Malaria* (Washington American Association for the Advancement of Science Smithsonian Institution Building 1941) p 255 The realization that quinine even in large doses could not be depended on for radical cure of malaria became clear when it was found that it failed to eliminate the extra erythrocytic cycle of the types of malignant *vivax* infection seen in the South Pacific in World War II (Ref 46)

44 TEMKIN Owsei and RAMSAY Elizabeth Antimalarial drugs Washington National Research Council Division of Medical Sciences issued by the Office of Medical Information 1944

At the beginning of World War II quinine was still the standard remedy for malaria and Atabrine was the only other known drug which had any noteworthy

Although an exo-erythrocytic cycle in bird malaria had been described as early as 1936 and in monkey malaria later (for review of the subject see C G Huff and F J Coulston "The development of Plasmodium galenaceum from sporozoite to erythrocytic trophozoite" J Infect Dis 75 231 1944) the human exo-erythrocytic cycle was first reported in a brief note by H E Shortt, P C C Garnham G Covell and P G Shute "The pre-erythrocytic stage of human malaria Plasmodium vivax" Brit M J 1:547 1948 The findings are described in more detail in the present paper It is pointed out that after "inoculation" malaria there is really no incubation period whereas after infection by mosquito bite there is a "clear cut incubation period varying in length according to the species of parasite" It is also noted that inoculation malaria can be promptly eradicated by drugs whereas "after sporozoite inoculation [by mosquito] the disease will make its appearance sooner or later in spite of the drug" All this strongly suggested a different sequence of infection with merozoites and sporozoites

A volunteer was bitten by a huge number of anopheles infected with *P vivax* and was also given an intravenous injection of an emulsion of infected mosquito salivary glands Seven days later *liver* biopsy showed "plasmodial masses studded with chromatin particles" which were interpreted as merozoites Interesting immunologic implications of the extra-erythrocytic cycle are also discussed.

Shortt, Fairley Covell, Shute and Garnham ("Pre-erythrocytic stages of Plasmodium falciparum" Tr Roy Soc. Trop Med & Hyg 44 405 1951) later described the pre-erythrocytic stage of *Plasmodium falciparum* in two volunteers Liver biopsies on the fourth, fifth and sixth days after inoculation showed beautifully the pre-erythrocytic schizonts in parenchymal cells

For a summary of the pertinent literature leading up to the whole question of the pre-erythrocytic and extra-erythrocytic cycle in man see N Hamilton Fairley's penetrating review (Ref 52) and P C C Garnham's authoritative summary with literature "Exo-erythrocytic schizogony in malaria" Trop Dis Bull. 45 831 1948 For a brief discussion see the recent article by P C C Garnham "The life history of the malaria parasite" in *Lectures on the Scientific Basis of Medicine* 2 323 (London Athlone Press 1954) Thus the sequence has been established in *vivax* malaria of the erythrocytic cycle (in man) the cycle in the mosquito the pre-erythrocytic cycle in man erythrocytic cycle again followed by exo-erythrocytic cycle in tissues

51 ALVING A S CRAIG Branch JONES Ralph Jr WHORTON C Merrill, PULLMAN Theodore N and EICHELBERGER, Lillian Pentaquine (Sn 13 276) a therapeutic agent effective in reducing the relapse rate in *vivax* malaria J Clin Investigation Vol 27, No 3 Part 2 p 25 1948

In a search for agents which might have a more potent curative effect the authors (*ibid* p 34) had conducted clinical trials with eighteen analogues of pamaquine Pentaquine seemed most promising The drug was tested in volunteers infected with *vivax* malaria While its effect in suppressing fever and parasitemia was not significantly different from quinine alone or quinine and pentaquine administered concurrently only one among thirty subjects suffered

out" or that crescents kept infection going Ross believed that "rallies" were due to extensive destruction of parasites by some immune process when this flagged parasites "escaped" and relapse occurred Many traumatic factors such as cold fatigue illness or excessive alcohol might be precipitating circumstances C F Craig the great American malariologist (A study of latent and recurrent malarial infection and the significance of intracorpuscular conjugation in the malarial plasmodia, J Infect Dis 4 108 1907) thought that "intra corpuscular conjugation" produced a resting stage of the plasmodia resistant to quinine which later gave birth to young plasmodia, thus causing a relapse This view was widely accepted The true explanation of relapses was not fully understood until the exo erythrocytic stage of the parasite in man was worked out (Ref 50)

47 MOST, H LONDON I M KANE C A LAVIETES P H SCHROEDER, E F and HAYMAN J M Chloroquine for treatment of acute attacks of vivax malaria J A M A 131 963, 1946

Chloroquine a 4 amino quinoline derivative turned out to be one of the most effective of the new synthetic antimalarials developed during the war Its properties were described in a statement approved by the Board for Coordination of Malarial Studies ("Activity of a new antimalarial agent Chloroquine [S N 7618] J A M A, 130 1069 1946) In clinical trials Most and his associates found it superior to quinine and quinacrine in acute attacks of *vivax* malaria This finding was generally accepted but Pullman and his associates soon showed that the relapse rate after treatment with quinine quinacrine and chloroquine was about the same 90 per cent or over (T N Pullman C Branch Jr A S Alving C M Whorton R Jones Jr and L Eichelberger Comparison of chloroquine quinacrine [Atabrine] and quinine in the treatment of acute attacks of sporozoite-induced *vivax* malaria [Chesson strain]" J Clin Investigation Vol 27, No 3 Part 2 p 46 1948) Hence the drug did not produce radical cure but it is an important survivor of the vast number of potential antimalarials tested

48 Symposium on biochemistry of malarial parasites Fed Proc 5 390 1946

Although the subject is outside the scope of this bibliography those interested will find here several papers which deal authoritatively with this part of the subject

49 MacDOUGALL, Mary Stuart Cytological studies of plasmodium the male gamete J Nat Malaria Soc 6 91 1947

The significance of the sexual forms gradually became clear through the work of MacCallum (Ref 24) and others (Ref 23) It is of interest that chromosomes seem now to have been definitely demonstrated in the various sexual forms Many interesting and important details are brought out in this paper by MacDougall

50 SHORTT H E and GARNHAM P C C The pre-erythrocytic development of Plasmodium cynomolgi and Plasmodium vivax Tr Roy Soc Trop Med & Hyg 41 785 1948

combined therapy with chloroquine for its suppressive effect with primaquine for radical cure This seems to be the most effective treatment today for malaria

Table 1 illustrates the development of drug therapy as outlined in References 47 and 51

TABLE 1

	S pp f Sympt m (Prophyl l)	C f Cl n al Attack	Rad l C (T ent f R l pse)
Quinine	+	+	0
Quinacrine (Atabrine)	++	++	0
Chloroquine Paludrine	+++	+++	0
Plasmochin (pamaquine)	±	±	+
Pentaquine	±	±	++
Primaquine	±	±	+++

This table is an oversimplification and doubtless will soon be modified by further work as new antimalarials are constantly being tested Meanwhile the subject of chemotherapy is brilliantly reviewed by N Hamilton Fairley "Malaria Lecture II Chemotherapy" Brit M J 2 891 1949

54 YOUNG Martin D Malaria during the last decade Am J Trop Med & Hyg 2 347 1953

This is a review of important recent contributions

a relapse Pentaquine was thought to be somewhat more effective than pamaquine in producing radical cure This work has been confirmed by others including L T Coggeshall and R A Rice (Cure of chronic vivax malaria with pentaquine J A M A 139 437 1949) and B Straus and J Gennis ("Evaluation of pentaquine as a cure of relapsing vivax malaria" Bull New York Acad Med 24 395 1948 "Radical cure of relapsing vivax malaria with pentaquine-quinine a controlled study Ann Int Med 33 1413 1950)

52 FAIRLEY N Hamilton Malaria, with special reference to certain experimental clinical and chemotherapeutic investigations Brit M J 2 825 1949

Innumerable observations on resistance and immunity may be culled from the early writings King (Ref 21), for example noted the resistance of African Negroes to malaria and thought that the pigmentation which gradually developed in white skins as the disease became chronic was a desirable event which indicated increased resistance Laveran (Ref 11 1891 p 175) recognized the fact that "cures called spontaneous that is without the use of quinine are not rare He believed following Metchnikoff that phagocytosis of parasites by leukocytes and macrophages was the essential factor in immunity Koch s remarks (Ref 32) are also of interest

Modern views on immunity are summarized by L T Coggeshall ("Immunity in malaria" Medicine 22 87 1943) but the position of the extra erythrocytic phase in immunity is more fully developed by Fairley in this lecture and by P C C Garnham and H E Shortt ("Demonstration of a persisting exo-erythrocytic cycle in Plasmodium cynomolgi and its bearing on the production of relapses" Brit M J 1 1225 1948) These workers believe that the anti parasitic defence mechanism of the host is directed against the erythrocytic cycle and not against pre erythrocytic or exo erythrocytic forms which seem to be protected against destruction by their situation in the liver cells They think that there is a "specific cellulo humoral response" to red cell invasion by the erythrocytic parasites Clinical immunity does not mean that every parasite is permanently cleared from the blood The parasites actually seem to be destroyed in various internal organs The relations of latency and relapse to immunity especially when the situation is modified by therapy therefore become excessively complicated Another interesting phase is specificity of immunity to species or even to strains This question is discussed by Coggeshall (*op cit*) and active work summarized by Young (Ref 54) is at present going on

53 GENNIS Joseph STRAUS Bernard KENNEY Michael and KLEIN Bernard The use of primaquine for the treatment of malaria in Korean veterans Am J Med 17 223 1954

Primaquine still another quinoline derivative was recently discussed in a comprehensive report to the Council on Pharmacy and Chemistry ("Status of primaquine" J A M A 149 1558 1952) Gennis and his associates described the use of this compound in Korean war veterans with *vivax* malaria One hundred and one patients were treated with only one relapse There were four recurrences (return of fever in less than 1 month after therapy) The writers advise therefore

Section 20

AMEBIC DYSENTERY

Amebic brain abscess	Ref 17
Amebic granuloma	Ref 27
Amebic liver abscess	Refs 1 2 9 10 11 13 18 19
Chemotherapy	Refs 24 26
Clinical	Refs 1 2 5 10 11
Cultivation of amebae	Ref 16
Cysts	Refs 12 14
Experimental amebiasis	Refs 8 12 20 21 25
General	Refs 1 2 10 11
Histology	Refs 7 11
Latent amebiasis	Refs 16 23
Parasitology	Refs 4 5 6 7 8 10 11 13 16
Toxicity of emetine	Ref 22
Treatment with emetine	Ref 19
Treatment with ipecac	Refs 3 18

"The influence of the moon in the production of dysentery as well as of fevers has been much discussed Th it dysentery and fever are both observed to supervene in a manner well calculated to authorize a belief in sol lunar influence cannot be denied by any experienced practitioner" (2 247) "On the subject also of the infectious nature of dysentery much has been advanced As the dis ease is met with in warm climates it seldom or never proves contagious" (2 249) Treatment consisted of bleeding purgation and various medicines among which ipecac is mentioned without special emphasis The volume con cludes with a series of beautiful colored plates of diseased bowels Those of the liver (Vol 1) in many cases picture indubitable amebic abscesses

William Twining s book *Clinical Illustrations of the Most Important Diseases of Bengal* (Calcutta Baptist Mission Press 1832) published a few years later covers essentially the same ground and contains little that is new concerning dysentery

2 PARKES E A Remarks on the dysentery and hepatitis of India London Longman Hunt Rees & Orme 1846

Parkes working in the Indian army medical service had plenty of opportunity to study dysentery and this book illustrates very well the rudimentary state of knowledge of the disease at the halfway mark of the century Nothing was known as to cause "I shall pass over this difficult subject rapidly as the causes of dysentery are as undetermined as its pathology" (p 131) There are men tioned the following "all acid agents suppression of secretions rapidly accom plished epidemic states of the atmosphere and alterations of blood" As to the great frequency of dysentery in India Parkes says that discounting all other possible causes "there still must remain to be accounted for an unusual prone ness in the mucous membrane of the large intestines to be acted upon by ex citing causes (p 132) Perhaps no individual ever can have during a life time opportunities of accurately studying all the varieties of dysentery —its com plications with remittent fever with cholera with gastro-enteritis and with typhus —its union with scurvy and purpura with several kinds of hepatitis with delirium tremens with pancreatic and spleen diseases its numerous chronic states depending on various stages of alteration hypertrophy ulceration or otherwise of the colonic and cecal solitary glands and thickening of the intesti nal coats (p 137) The association of dysentery with hepatic abscess is clearly recognized but it is not known which causes the other or indeed which really comes first "The causes of primary hepatitis meaning by that term the low in sidious supperative form generally in an advanced stage complicated with dysentery are much more obscure The first opinion which claims our attention is that which refers the disease to the action of external heat (p 229) Under treatment stress is laid on depletion—bleeding—plus a great variety of medicines Parkes does point out however that the "large doses of ipecacuanha viz from 30 grs to 1 dr are much more efficacious th in smaller doses (p 145) Parkes s objective descriptions of clinical cases and autopsies are however refreshing in the midst of otherwise arid material

Finally how much of Parkes s dysentery was bacillary and how much was amebic remains a puzzle There had been little progre s since Annesley s vast monograph in 1828 (Ref 1)

Section 20

AMEBIC DYSENTERY

THE subject of amebic dysentery and amebiasis is systematically covered in a wide variety of textbooks and monographs Leonard Rogers *Dysenteries Their Differentiation and Treatment* (London Henry Frowde 1913) gives an authoritative discussion with an excellent historical review and a good selected bibliography Other recent books of note are those by C F Craig *The Etiology Diagnosis and Treatment of Amebiasis* (Baltimore Williams & Wilkins Co 1944) by H H Anderson W L Bostick, and H G Johnstone *Amebiasis Pathology Diagnosis and Chemotherapy* (Springfield Ill Charles C Thomas 1953) with extensive references to the recent literature and by E C Faust *Amebiasis* (Springfield, Ill Charles C Thomas 1954) which gives a concise outline of the subject Books on the parasitology of amebiasis suitable for the general reader are those of C Dobell *The Amoebae Living in Man* (London John Bale Sons & Danielsson Ltd 1919) and of C Dobell and F W O Connor *The Intestinal Protozoa of Man* (London John Bale & Danielsson Ltd 1921) A somewhat more comprehensive treatise is that of M Hartmann and C Schilling *Die pathogenen Protozoen* (Berlin Julius Springer 1917)

1 ANNESLEY James Researches into the causes nature and treatment of the more prevalent diseases of India and of warm climates generally 2 vols London Longman Rees Orme Brown & Green 1828

One cannot neglect in the bibliography of amebic dysentery Annesley s two monumental folio volumes This is indeed a magnum opus The author says in his Preface *"To this end he has sedulously watched disease throughout its* course and when it proved fatal compared the symptoms while living with the appearances after death (p xiv) This is the keynote of the book which deals less with vague speculations than with descriptions of observed facts The elaborate section on hepatic abscess (1 516) first gives a general discussion followed by case reports It [hepatic inflammation] frequently supervenes to the insidious inflammation of the substance of the liver which often accompanies if it does not actually occasion a particular variety of dysentery " As to dysentery (2 151 chap v) he says "In the observations which we shall have to make on this very important and prevalent disease *we shall first consider it in its simpler or less* complicated forms we shall next treat of that variety which is characterized by attendant disorder of the liver and afterwards offer some remarks on the chronic forms of the disease and on the scorbutic dysentery which is occasionally met with in intertropical practice" (1 151) He gives an excellent description of acute dysentery but whether bacterial or amebic one cannot be sure Section II deals with "Hepatic Dysentery or Dysentery Complicated with Disease of the Liver " and this is almost surely amebic "Hepatic dysentery assumes various forms or modifications it is sometimes acute but much more frequently sub-acute and chronic" (1 197) Like other observers at the time Annesley was confused about the relation of dysentery and liver abscess he was uncertain which came first and which was the cause of the other His speculations on the cause of dysentery are disappointing in contrast to his description of cases

peculiar motility" While the amebae were for a long time a constant finding from March 11 on "despite the greatest care no more amebae were demonstrated throughout his course" A beautiful description of the parasites is given dealing with structure size motility nucleus etc Losch does not however emphasize the presence of red blood cells in the parasites "Aside from the nucleus the vacuoles and the granules one observes not uncommonly in the protoplasm various formed particles taken up from the outside bacteria vibrios chains of mycothrix cocci and exceptionally larger elements such as red and white blood corpuscles" Losch suggests the name *Amoeba coli* because the colon seemed to be its principal site and because it was unlike any hitherto described ameba The pictures given in his Plate X are excellent again the absence of red cells in the parasites is striking The autopsy findings were those of an advanced cicatricial colitis the lower ileum was also involved "The thickening and swelling of the mucous membrane of the colon depended as microscopic examination showed mainly upon an inflammatory infiltration of the submucosa"

Losch after trying numerous medicaments decided to use quinine because he found that a solution of quinidine 1-5 000 in vitro killed the amebae in 1 minute at least they became motionless round and granular Losch used the quinine in a clyster 20 gm to the pound of water after which the amebae disappeared from the stools for several days but soon reappeared This observation was however the start of chemotherapy for amebiasis although all the early efforts were with solutions used locally rather than systematically

Losch analyzed the case in relation to the amebae and concluded "One must therefore assume that Markow sickened first with dysentery and that only later did the amebae enter the bowel and grow there and there maintained the inflammation"

Is this suggestion of Losch correct? It must be admitted that the clinical features—a sporadic case in a cool climate the long duration with remissions and exacerbations the character of the stools the final disappearance of the amebae—suggest ulcerative colitis rather than amebic dysentery However the huge numbers of amebae are hard to explain in any other than a causal role even though the paucity of ingested red cells is striking

Losch also reports some experiments in which he fed to dogs or injected into the rectum stools from the patient Three of four experiments were "entirely negative The results in the fourth are hard to interpret Globules of mucus adhering to particles of formed stool contained many amebae some days after inoculation The animal did not seem ill and was sacrificed on the eighteenth day There were three superficial ulcerations in the rectum It is impossible to say whether Losch really produced amebic dysentery but subsequent writers usually found dogs refractory to the experimental disease

The exact interpretation of Losch s case is therefore not entirely clear

6 KARTULIS [S] Zur Aetiologie der Dysenterie in Aegypten Virchows Arch f path Anat **105** 521 1886

Kartulis was evidently alert to the possibility of amebae in stools because he raised the question in connection with certain bodies which he found ("Ueber Riesen Amoben[?] bei chronischer Darmentzundung bei Aegypter" *ibid* **99** 145 1885) in the stools of a boy who had had dysentery several months previously It is obvious from the description and the drawing that these bodies

3 DOCKER, E S On the treatment of dysentery by the administration of large doses of ipecacuanha Lancet, 2 113, 1858

We cannot trace in detail the introduction of ipecac into the treatment of tropical dysentery Apparently the drug was in common use however in India by the beginning of the nineteenth century Docker working in Mauritius seems however to deserve the credit for using ipecac in really large and effective doses "Out of upwards of fifty cases of dysentery I lost but one (in four years the mortality ranged from ten to eighteen percent) " He points out the "ineffectiveness" of the small amounts commonly employed. I give it in doses ranging from ten to ninety grains In all constitutions robust as well as delicate under all circumstances the result is the same In the very worst cases after the whole range of remedies has been tried in vain the disease running its course swiftly and surely to a fatal issue ninety grains of ipecacuanha have been given and forthwith the character of the disease or I should rather say the character of the *symptoms* has been entirely changed for the disease itself is literally cured put a summary stop to driven out" Striking illustrative cases are presented

4 LAMBL, Wilhelm Mikroscopische Untersuchungen der Darm Excrete Vrtljschr f d prakt Heilk. 1 1 1859

Lambl is usually mentioned as the first observer concerned with amebae in the stools In this paper however which deals in detail with the character of the stools in disease no mention is made of amebae nor is anything resembling them shown in the illustrations Under the heading of "Intestinal Parasites" only larger parasites such as tapeworms are mentioned In Lambl's second communication (I Theil *Beobachtungen und Studien aus dem Gebiete der pathologischen Anatomie und Histologie* [Prague Friedrich Tempsky 1860]) he was no more definite as his illustration (reproduced in Stilwell *op cit*) shows Whatever the bodies pictured may be they are certainly not amebae

5 LOSCH F Massenhafte Entwickelung von Amoeben im Dickdarm Virchows Arch f path Anat 65 196 1875

The famous case of Losch is supposed to be the first well-described instance of amebic dysentery It concerned J Markow a peasant who was taken sick in St Petersburg in the summer of 1871 with a stubborn diarrhea which persisted for several months The story is that of relapses and remissions until his death in the hospital after a period of nearly 3 years The stools were largely pus blood and mucus but at times they were profuse and watery The patient became weak pale and edematous and death occurred on April 12 "with the picture of severe anemia and general exhaustion It is of interest that Professor Eichwald because of the anemia suggested a transfusion which was performed on February 11 by Dr Roussel "with the apparatus constructed by him and 9 ounces of blood drawn from the median cephalic vein of a strong healthy man were injected directly into the cephalic vein of the upper arm of the patient" Right after this transfusion a chill occurred lasting half an hour followed by a feeling of heat The temperature rose in three hours to 40 1 but by evening fell to 38 5 "The stools showed in large numbers as many as 60 to 70 or more per field some free some enclosed in mucus large cell like structures which were immediately to be recognized as parasites in fact amebae because of their

peculiar motility" While the amebae were for a long time a constant finding from March 11 on "despite the greatest care no more amebae were demonstrated throughout his course" A beautiful description of the parasites is given dealing with structure size motility nucleus etc Losch does not however emphasize the presence of red blood cells in the parasites Aside from the nucleus the vacuoles and the granules one observes not uncommonly in the protoplasm various formed particles taken up from the outside bacteria vibrios chains of mycothrix cocci and exceptionally larger elements such as red and white blood corpuscles" Losch suggests the name *Amoeba coli* because the colon seemed to be its principal site and because it was unlike any hitherto described ameba The pictures given in his Plate X are excellent again the absence of red cells in the parasites is striking The autopsy findings were those of an advanced cicatricial colitis the lower ileum was also involved "The thickening and swelling of the mucous membrane of the colon depended as microscopic examination showed mainly upon an inflammatory infiltration of the submucosa"

Losch after trying numerous medicaments decided to use quinine because he found that a solution of quinidine 1-5 000 in vitro killed the amebae in 1 minute at least they became motionless round and granular Losch used the quinine in a clyster 20 gm to the pound of water after which the amebae disappeared from the stools for several days but soon reappeared This observation was however the start of chemotherapy for amebiasis although all the early efforts were with solutions used locally rather than systematically

Losch analyzed the case in relation to the amebae and concluded "One must therefore assume that Markow sickened first with dysentery and that only later did the amebae enter the bowel and grow there and there maintained the inflammation"

Is this suggestion of Losch correct? It must be admitted that the clinical features—a sporadic case in a cool climate the long duration with remissions and exacerbations the character of the stools the final disappearance of the amebae—suggest ulcerative colitis rather than amebic dysentery However the huge numbers of amebae are hard to explain in any other than a causal role even though the paucity of ingested red cells is striking

Losch also reports some experiments in which he fed to dogs or injected into the rectum stools from the patient Three of four experiments were entirely negative" The results in the fourth are hard to interpret Globules of mucus adhering to particles of formed stool contained many amebae some days after inoculation The animal did not seem ill and was sacrificed on the eighteenth day There were three superficial ulcerations in the rectum It is impossible to say whether Losch really produced amebic dysentery but subsequent writers usually found dogs refractory to the experimental disease

The exact interpretation of Losch s case is therefore not entirely clear

6 KARTULIS [S] Zur Aetiologie der Dysenterie in Aegypten Virchows Arch f path Anat **105** 521 1886

Kartulis was evidently alert to the possibility of amebae in stools because he raised the question in connection with certain bodies which he found (Ueber Riesen Amoben[?] bei chronischer Darmentzundung bei Aegypter ibid 99 145 1885) in the stools of a boy who had had dysentery several months previously It is obvious from the description and the drawing that these bodies

queried by Kartulis himself are not amebae at all But a year later Kartulis unequivocally described amebae which were found in every case of undoubted dysentery In no cases [of other disease] could I find amebae There is a splendid description of the organisms which leaves no doubt as to their nature although Kartulis mentions slight differences between his and Losch s (Ref 5) amebae Kartulis went beyond Losch in describing amebae in stained sections of bowel Alcoholic solutions of methylene blue and gentian violet were especially suitable The parasites were seen most abundantly in fresh ulcers In several preparations the amebae were present in such numbers that the whole submucosa seemed full of them " "Their form in sections is usually round or oval " Kartulis was unable to cultivate the amebae He found them dead in 24 hours and in sugar or salt water they died in a few hours In hanging drop they survived for 12 hours Introduction into the colons of two guinea pigs and one rabbit was without result The amebae were found in all stages of dysentery "That the amebae must be accepted as the cause of tropical dysentery seems definite on the basis of what has been reported But how the organisms enter and succeed in developing in the colon is hard to explain Kartulis work is impressive and he clearly established amebae as the cause of dysentery although his finding of their invariable presence in dysentery and invariable absence in other diseases is perhaps to be questioned Later N G Masiutin (Ob amoebakh kak tchougeiadnykh tolotiakh kislok Vrach 10 557 1889[1] German abstract Ueber die Amoeben als Parasiten des Dickdarms " Centralbl f Bakt 6 451 1889) found amebae similar to those of Losch in five cases of various bowel disturbances including one of "typhoid" fever For this reason he doubted the primary etiological role of amebae but suggested that they entered the body in drinking water multiplied and were a factor in keeping up a disease process caused by some other agent Like his predecessors he prescribed clysters of various substances of which he regarded quinine as the most effective in extirpating the amebae and allowing the disease process to subside Kartulis ("Ueber weitere Verbreitungsgebiete der Dysenterie Amoeben " Centralbl f Bakt 7 54 1890) disputed Masiutin s doubts about the causal role of amebae and reported two cases of dysentery which he examined on a visit to Greece in the discharges of which the same amebae were found as those he had seen in Egypt He thought that Masiutin s observations simply widened the field of symptom complexes which could be produced by these amebae One gets the picture of the doubts and speculations of the early observers as to the true role in disease of these animalcules

7 KOCH Robert Bericht uber die Thatigkeit der zur Erforschung der Cholera im Jahre 1883 nach Egypten und Indien entsandten Kommission Arb a d k Gsndhtsamte Vol 3 Anlage VI p 63 1887

Koch made careful autopsies as early as 1883 not only on cholera patients but on people dead of other diseases there were five instances of dysentery two of which were complicated by liver abscess "There were found in the bases of fresh ulcers [in the colon] in addition to innumerable bacteria peculiar ameba like structures These bodies were seen only in sections of the ulcers or in material taken from them rather than in the stools a fact which indicated to

[1] I am indebted to Mrs A Hoen for the correct transcription of this title from the original Russian

Koch "a close relation to disease" Amebae were also seen in the capillaries near a liver abscess Koch was evidently the first to recognize amebae in stained sections of tissue but he does not seem to have pursued the matter further himself although Kartulis his pupil acknowledged Koch s influence (Ref 6)

8 HLAVA Jaroslav O uplavici předběžné sdělení Časop lék cesk **26**:70 1887 (Abstract by Kartulis Centralbl f Bakt **1**:537 1887)

We have not seen the original article which is described in the interesting paper by G G Stilwell ("Amoebiasis its early history" Gastroenterology **28**:606 1955) together with the error which Kartulis made in his abstract in setting down O Uplavici (on dysentery) as the author s name Hlava had sought for bacteria in the stools of dysentery patients but as he had convinced himself that no constant bacterial form was present he looked for amebae In sixty cases partly sporadic, partly endemic he always found amebae in the fresh stools He injected ameba-containing stools into the rectums of seventeen dogs with two positive results of six cats with four positive results and of a number of rabbits chickens and guinea pigs with no reaction Since dysentery was transmissible to cats the writer concluded that the ameba was the cause of dysentery Finally he reports a case with giant amebae with which he infected a cat and again recovered giant amebae from it These observations were carried on in Prague not in the tropics and one cannot help feeling some reservations about them It is however of interest that cats or at least kittens have turned out to be the most satisfactory animals for experimental amebiasis

In setting the record straight about Dr Hlava one should refer to C Dobell s article "Dr O Uplavici (1887–1938)" Parasitology **30** 239 1938 where this comedy of errors is fully explained

9 KARTULIS [S] Zur Aetiologie der Leberabscesse Lebende Dysenterie Amoeben im Eiter der dysenterischen Leberabscesse Centralbl f Bakt **1** 681 1887

"The constant finding of amebae in every case of dysentery impelled me to look for them in the liver abscesses which complicate this disease Amebae were found in all of twenty cases Kartulis reports an instance in which the abscess had ruptured into the pleura the patient died shortly after thoracotomy The pus at autopsy from an intact liver abscess showed the amebae "practically in pure culture" Bacterial cultures were made in four cases and various organisms were obtained Kartulis regarded these as secondary invaders which entered with the amebae A little later (Ueber tropische Leberabscesse und ihr Verhaltniss zur Dysenterie Virchows Arch f path Anat **118** 97 1889) he discussed critically the whole subject of tropical liver abscess in relation to dysentery He concluded "From what has been said it seems probable that in Egypt amebae play an etiological role in the genesis of dysenteric liver abscess and that pyogenic bacteria probably originating in the gastro intestinal tract cause idiopathic liver abscess"

There is an immense literature on hepatic amebiasis which we cannot review further the reader is referred to sections on the subject in all the books to which reference is made in the introduction Recently however N J Conan Jr ("The treatment of hepatic abscess with chloroquine" Am J Med 6 309 1949) recommends chloroquine as a specific his work is confirmed by W A Sodeman

quened by Kartulis himself are not amebae at all But a year later Kartulis unequivocally described amebae which were found in every case of undoubted dysentery In no cases [of other disease] could I find amebae" There is a splendid description of the organisms which leaves no doubt as to their nature although Kartulis mentions slight differences between his and Losch s (Ref 5) amebae Kartulis went beyond Losch in describing amebae in stained sections of bowel Alcoholic solutions of methylene blue and gentian violet were especially suitable The parasites were seen most abundantly in fresh ulcers "In several preparations the amebae were present in such numbers that the whole submucosa seemed full of them" "Their form in sections is usually round or oval" Kartulis was unable to cultivate the amebae He found them dead in 24 hours and in sugar or salt water they died in a few hours In hanging drop they survived for 12 hours Introduction into the colons of two guinea pigs and one rabbit was without result The amebae were found in all stages of dysentery "That the amebae must be accepted as the cause of tropical dysentery seems definite on the basis of what has been reported But how the organisms enter and succeed in developing in the colon is hard to explain" Kartulis work is impressive and he clearly established amebae as the cause of dysentery although his finding of their invariable presence in dysentery and invariable absence in other diseases is perhaps to be questioned Later N G Masiutin ("Ob amoebakh kak tchougeiadnykh tolotiakh kislok" Vrach 10 557 1889[1] German abstract "Ueber die Amoeben als Parasiten des Dickdarms" Centralbl f Bakt 6 451 1889) found amebae similar to those of Losch in five cases of various bowel disturbances including one of "typhoid" fever For this reason he doubted the primary etiological role of amebae but suggested that they entered the body in drinking water multiplied and were a factor in keeping up a disease process caused by some other agent Like his predecessors he prescribed clysters of various substances of which he regarded quinine as the most effective in extirpating the amebae and allowing the disease process to subside Kartulis ("Ueber weitere Verbreitungsgebiete der Dysenterie Amoeben" Centralbl f Bakt 7 54 1890) disputed Masiutin s doubts about the causal role of amebae and reported two cases of dysentery which he examined on a visit to Greece in the discharges of which the same amebae were found as those he had seen in Egypt He thought that Masiutin s observations simply widened the field of symptom complexes which could be produced by these amebae One gets the picture of the doubts and speculations of the early observers as to the true role in disease of these animalcules

7 KOCH Robert Bericht uber die Thatigkeit der zur Erforschung der Cholera im Jahre 1883 nach Egypten und Indien entstandten Kommission Arb a d k Gsndhtsamte Vol 3, Anlage VI p 63 1887

Koch made careful autopsies as early as 1883 not only on cholera patients but on people dead of other diseases there were five instances of dysentery two of which were complicated by liver abscess "There were found in the bases of fresh ulcers [in the colon] in addition to innumerable bacteria peculiar ameba like structures These bodies were seen only in sections of the ulcers or in material taken from them rather than in the stools a fact which indicated to

[1] I am indebted to Mrs A Hoen for the correct transcription of this title from the original Russian

Koch "a close relation to disease " Amebae were also seen in the capillaries near a liver abscess Koch was evidently the first to recognize amebae in stained sections of tissue but he does not seem to have pursued the matter further himself although Kartulis his pupil acknowledged Koch s influence (Ref 6)

8 HLAVA Jaroslav O uplavici předběžné sdělení Časop lék cesk **26** 70 1887 (Abstract by Kartulis Centralbl f Bakt **1**:537 1887)

We have not seen the original article which is described in the interesting paper by C G Stilwell ("Amoebiasis its early history" Gastroenterology **28** 606 1955) together with the error which Kartulis made in his abstract in setting down O Uplavici (on dysentery) as the author s name Hlava had sought for bacteria in the stools of dysentery patients but as he had convinced himself that no constant bacterial form was present he looked for amebae In sixty cases partly sporadic partly endemic he always found amebae in the fresh stools He injected ameba-containing stools into the rectums of seventeen dogs with two positive results of six cats with four positive results and of a number of rabbits chickens and guinea pigs with no reaction Since dysentery was transmissible to cats the writer concluded that the ameba was the cause of dysentery Finally he reports a case with giant amebae with which he infected a cat and again recovered giant amebae from it. These observations were carried on in Prague not in the tropics and one cannot help feeling some reservations about them It is however of interest that cats or at least kittens have turned out to be the most satisfactory animals for experimental amebiasis

In setting the record straight about Dr Hlava one should refer to C Dobell s article "Dr O Uplavici (1887–1938) " Parasitology **30** 239 1938 where this comedy of errors is fully explained

9 KARTULIS [S] Zur Aetiologie der Leberabscesse Lebende Dysenterie Amoeben im Eiter der dysenterischen Leberabscesse Centralbl f Bakt **1** 681 1887

"The constant finding of amebae in every case of dysentery impelled me to look for them in the liver abscesses which complicate this disease " Amebae were found in all of twenty cases Kartulis reports an instance in which the abscess had ruptured into the pleura the patient died shortly after thoracotomy The pus at autopsy from an intact liver abscess showed the amebae "practically in pure culture " Bacterial cultures were made in four cases and various organisms were obtained Kartulis regarded these as secondary invaders which entered with the amebae A little later ("Ueber tropische Leberabscesse und ihr Verhaltniss zur Dysenterie " Virchows Arch f path Anat **118** 97 1889) he discussed critically the whole subject of tropical liver abscess in relation to dysentery He concluded "From what has been said it seems probable that in Egypt amebae play an etiological role in the genesis of dysenteric liver abscess and that pyogenic bacteria probably originating in the gastro-intestinal tract, cause idiopathic liver abscess "

There is an immense literature on hepatic amebiasis which we cannot review further the reader is referred to sections on the subject in all the books to which reference is made in the introduction Recently however N J Conan Jr ("The treatment of hepatic abscess with chloroquine" Am J Med **6** 309 1949) recommends chloroquine as a specific his work is confirmed by W A Sodeman

A A Dolvinen E M Gordon and C M Gilikin "Chloroquine in hepatic amebiasis" Ann Int Med 35:331, 1951

10 OSLER William On the Amoeba coli in dysentery and in dysenteric liver abscess Bull Johns Hopkins Hosp 1 53 1890

Osler was the first on this side of the Atlantic to describe amebae in dysentery and liver abscess "Dr B age 29, resident in Panama for nearly six years had a chronic dysentery he began to have an irregular fever with occasional chilly sensations and sweats, to lose flesh and to have a very sallow complexion. He had six or eight mucoid stools with traces of blood daily" Liver abscess was diagnosed and evacuated surgically Osler found in the pus "in large numbers the amoebae which Kartulis had described The material was taken at once to the Pathological Laboratory where Prof Welch and Dr Councilman confirmed the observation After the operation the dysenteric symptoms did not abate in the slightest, he continued to have from eight to sixteen movements daily" Osler then gives a detailed description of the amebae drawings of which are reproduced for the first time in Stilwell's article (Ref 8) Osler concluded "It is impossible to speak as yet with any certainty as to the relation of these organisms to the disease The subject is deserving of extended study and a point of special interest will be the determination of their presence in the endemic dysentery of this country"[2] Shortly after Lafleur ("Demonstration of Amoeba coli in dysentery" Bull Johns Hopkins Hosp 1 91 1890) reported a case of dysentery in a sailor on a steamship sailing between Baltimore and Bremen "in which the Amoeba coli had been found in the stools and exhibited the living parasite under the microscope" The patient had been in the tropics in 1880 A third case was soon reported by Simon ("Abscess of the liver perforation into the lung Amoeba coli in sputum" Bull Johns Hopkins Hosp 1:97 1890) The patient had been in the West Indies in 1883 but was quite well when there He developed diarrhea and cough and "on the day of admission the expectoration was noticed to be a peculiar rustry reddish brown color purulent and resembling anchovy sauce Actively moving amoebae were found in it, a fact which at once called attention to the bowels and to the liver Our attention would never have been called to his actual condition by the character of the stools As they looked perfectly healthy with simply adherent mucus we should probably have regarded the case as one of pleurisy" The atmosphere at Johns Hopkins thus was ripe for the work of Councilman and Lafleur (Ref 11)

From now on there are various confirmatory reports of the presence of amebae in dysentery and liver abscess They are carefully reviewed by Councilman and Lafleur

On March 20 Osler wrote to Musser as follows "We have been much excited over Kartulis amoebae which we have found in a liver abscess from a case of dysentery —a Dr from Panama They are most extraordinary & striking creatures & take one's breath away at first to see these big amoebae—10–20 times the size of a leucocyte—crawling about in the pus The movements are very active & in one case kept up for 10 hours I get a fresh stock of pus from the drainage tube every day so if you could run down some eve we could look for the creatures in the morning Keep an eye on your Blockley dysenteries as it would be most interesting to find similar bodies in our dysenteries" (Harvey Cushing *The Life of Sir William Osler* [Oxford 1926] 1 326)

11 COUNCILMAN W T and LAFLEUR H A Amoebic dysentery Johns Hopkins Hosp Rep 2 395 1891

This monograph of some hundred and fifty pages stimulated by the cases seen at Johns Hopkins (Ref 10) is indeed a landmark in the study of the subject "In this article we propose to consider a disease which is characterized by definite pathological lesions and is separated not only by its destructive pathological anatomy but also by its aetiology and clinical history from other affections of the intestines with which it has hitherto been classed under the general name of dysentery Councilman and Lafleur were therefore the first unequivocally to define amebic dysentery as a specific disease and indeed to give it a specific name and to rename its causal agent *Amoeba dysenteriae* They give a detailed description of the parasites and emphasize the presence in them of red blood cells "as many as six or eight having been seen in a single amoeba" They describe and picture the appearance of dead amebae stained in various ways They report fifteen cases of amebic dysentery and give a classical clinical analysis of every feature of the disease The section on hepatic abscess is specially important and they point out the frequency of this complication in patients who have no overt dysentery In short modern study has added little to this definitive analysis As to therapy "Ipecacuanha was administered in case VIII after the manner recognized by surgeons in India" and in other cases "quinine was given by mouth on theoretical grounds rather than from empirical evidence as to its value" Clysters of quinine as well as of bichloride of mercury 1 5 000 or 1 3 000 were employed in two cases and each injection was retained for 10-15 minutes The results achieved are not brilliant but warrant a more extended trial This much can be said that quinine injections do destroy amoebae in the contents of the bowel but whether they reach and destroy the amoebae in the tissues is an open question The section in which the pathological lesions are meticulously described is one of the outstanding features of this monograph. The writers thought that the amebae produced a necrosis of tissue and exercised a solvent effect on the intercellular substance "The ulceration is produced by infiltration of the submucous tissue and necrosis of the overlying mucous membranes the ulcer *in consequence having the undermined form Frequently in* addition to the ulcers there is infiltration of the submucous tissue without ulceration In all of these lesions unless complicated by the action of bacteria there is absence of the products of purulent inflammation" "These abscesses [of the liver] differ in their anatomical features from those produced by other causes The chief difference is found in the absence of purulent inflammation the abscess being caused by necrosis softening and liquefaction of the tissue In these liver abscesses the amoebae are not associated with any other organism" "This is the form of dysentery which has been commonly called tropical dysentery" There are numerous reproductions of microscopic sections of the lesions and colored drawings of stained amebae showing their structure There is a bibliogaphy of 98 pertinent titles

In short this monograph is a definitive account of the disease to date which has hardly been superseded today

12 QUINCKE H and ROOS E I Ueber Amoeben Enteritis Berl klin Wchnschr 30 1089 1893

Quincke and Roos made notable contributions to the subject They were the first to describe cysts "Of special importance is the encysted condition of the ame bae These forms are considerably smaller have a diameter of 10–12 μ a much sharper if not definitely doubled contour *they appear shiny transparent* and show the nucleus very unclearly " "Very noteworthy is the great *Haltbarkeit* of these encysted forms in the moist chamber as well as in the stools they could still be recognized after 20 days but not after 4–8 weeks " Whereas the vegeta tive forms injected into the rectum of kittens caused dysentery they were harm less when given by mouth on the other hand the cysts produced disease when fed Another important finding was the discovery of other amebae in the bowel definitely different from those associated with severe dysentery "There are similar but milder forms of endemic dysentery the parasite causing them (*Amoeba coli mitis*) is different from the *Amoeba coli* of Losch and is not pathogenic for kittens One ameba often found in healthy people and doubtless harmless (*A intestinalis vulgaris*) is probably different from both " A little later Roos ("Zur Kentniss der Amoebenenteritis Arch f exper Path u Pharmakol 33 389 1894) pursued the subject further He reports elaborate observations on production of dysentery in cats by rectal instillation of material containing amebae and by introducing cysts into the stomach On the other hand no dis ease was produced by stools containing *A coli mitis* "According to our experi ments infection with the parasites probably results from the ingestion of cysts of amebae by mouth " This work was later confirmed by R P Strong and W E Musgrave ("Preliminary note regarding the etiology of the dysenteries in Manila " Rep of the Surg Gen of the Army Washington 1900 p 251) Quincke and Roos therefore opened the way to the discovery of the mode of transmission of amebic dysentery

Meanwhile there appeared a comprehensive review by A Schulberg ("Die parasitischen Amoben des menschlichen Darmes " Centralbl f Bakt 13 598 654 701 1893) with a subtitle of "Critical Review of the Development of Cur rent Knowledge Schulberg analyzes the conflicting claims in the literature with regard to the pathogenicity of amebae found in the bowel with a bibliography of some fifty titles

13 KRUSE W and PASQUALE A *Untersuchungen uber Dysenterie und Leberabscess Ztschr f Hyg u Infectionskr 16 1 1894*

In this tremendous communication of 149 pages on amebic dysentery and liver abscess Kruse and Pasquale reported confirmation of much of the earlier work as well as many experiments in which the disease was successfully transmitted to kittens They used pus from liver abscesses and produced dysentery in three experiments In two of these three experiments pus was used which the micro *scope and culture showed was completely sterile apart from the amebae* " Thus they made the important observation that amebae alone could produce dysen tery without the associated activity of bacteria as many had insisted Indeed at the time the view was prevalent that amebae were opportunists which took advantage of existing lesions to invade and aggravate them Thus as keen an observer as George Dock ("Observations on the Amoeba coli in dysentery and abscess of the liver " Texas M J 6 419 1891) after finding amebae in a variety of apparently poorly related conditions concluded "We have no reason for

ascribing pathogenic powers to the parasite though the evidence is such that it offers a promising field for future investigations"

14 HUBER [Demonstration of dysentery amebae] Deutsche med Wchnschr 29 267 1903

"Further I would like to call attention to one important finding namely small delicate spherical cysts which I must conclude are *encysted forms of the* amebae Every time when the patient s stool became hard and the amebae dis appeared these cysts appeared and when a relapse occurred and amebae were again present in the stools the cysts disappeared Furthermore I have been able to infect animals per os with such cyst containing stools The cysts found by me are distinguished from those of the ordinary ameba which Schau dinn has exactly described Unstained the nucleus is very hard to recognize In stained preparations the nucleus is more prominent as a delicate chromatin poor ring On occasion one finds two or four nuclei"

With this classic description Huber amplified that of Quincke and Roos (Ref 12) He pursued the subject further in a more comprehensive article "Unter suchungen uber Amobendysenterie" Ztschr f klin. Med 67 262 1909

15 SCHAUDINN Fritz Untersuchungen uber die Fortpflantzung einiger Rhizopoden (vorlaufige Mittheilung) Arb a d k. Gsndhtsamte 19 547 1903

Fritz Schaudinn the great discoverer of the spirochete of syphilis erred badly in his interpretation of the life cycle of amebae as he had in his studies of the invasion of red cells by sporozoites in malaria Part of his work on the vegeta tive forms of amebae was sound and he coined the name *Amoeba histolytica* "I choose to call them *Entamoeba histolytica* because of their capacity to destroy tissue" But he went wrong in his interpretation of encystment and his belief that he had demonstrated multiplication by sporulation Schaudinn s authority confused the subject for many years the details of the story are given in Stil wells article (Ref 8)

16 MUSGRAVE W E and CLEGG Moses T Amebas their cultivation and etiological significance Manila Bureau of Government Laboratories October 1904

Musgrave and Clegg first review the conflicting literature on attempts to grow amebae outside the body They succeeded with various strains on a medium the base of which was agar sodium chloride and extract of beef provided that the amebae were grown in symbiosis with pure cultures of bacteria which favored their development "Amebas are the etiologic factors in the disease generally known as amebic dysentery and by following the methods described in this paper such amebas may be grown on artificial media and the disease reproduced in monkeys and man by the ingestion of these cultures Amebas may be reclaimed by culture from the stools or the intestinal ulcers" The authors concluded "All amebas are or may become pathogenic This proposi tion pending a complete solution of the problem is the only safe one to adopt from the standpoint of public health in the Tropics" Musgrave and Clegg also introduced the term "amebiasis" "The term amebiasis which has been intro- duced in this article denoting an infection with amebas is comparable in its

application to filariasis trypanosomiasis uncinariasis etc It is not open to the objections so frequently offered to amebic dysentery amebic enteritis and the other names usually given to the disease" Musgrave ("Intestinal amoebiasis without diarrhoea," Philippine J Sc 5B 229 1910) later reported patients who had died of various conditions mostly unrelated to amebic infection and usually without bowel symptoms but who at autopsy showed "characteristic amoebic lesions" *Such symptoms as abdominal "aching" flatulence* constipation distention and loss of weight were noted in some patients "When we come to study the clinical phenomena shown by this class of cases it is seen that there is nothing specific or definite in any one, or in all the findings except the one of the presence of amoebae in the stools"

E L Walker ("A comparative study of the amoebae in the Manila water supply in the intestinal tract of healthy people and in amoebic dysentery" Philippine J Sc 6B:259 1911) had been working on the problem of amebae for some years "It has been my experience that if the character of both the trophozoite and the cyst be taken into consideration they can always be separated into species having well defined morphological characteristics" He was able to confirm Musgrave and Clegg in so far as it was possible to cultivate amebae by their methods but only non pathogenic amebae were derived from the Manila water supply "The amoeboid organisms parasitic in the intestinal tract of man belong to a distinct genus *Entamoeba* The entamoebae are strict or obligatory parasites and are incapable of multiplication outside the body of the host They cannot be cultivated on Musgrave and Clegg's medium" Walker emphasized the morphological differences between *Entamoeba histolytica* and the harmless *E coli* "The infection with *Entamoeba histolytica* may persist for an indefinite period after the symptoms of amoebic dysentery have disappeared during which time the resistant encysted entamoebae may be passed in large numbers in the stools and constitute an important source of infection to others Such persons are carriers of amoebic dysentery comparable to the carriers of typhoid fever or cholera The prophylactic measures for the prevention of amoebic dysentery are sufficiently indicated by the preceding conclusions they are identical with those required for prevention of other specific infectious diseases of the intestinal tract like typhoid fever and cholera" There are reproductions of excellent drawings of the various types of amebae The importance of Walker's observations cannot be overestimated

While the work of Musgrave and Clegg was not generally accepted D W Cutler ("A method for the cultivation of *Entamoeba histolytica*" J Path. & Bact 22 22 1918) described a method "by which *E histolytica* can be maintained in culture for several months These cultures if inoculated into cats produce dysenteric lesions of the intestines" He found that cysts could be produced in cultures by omitting to subculture for 4 or 5 days W C Boeck and J Drbohlav ("The cultivation of Endamoeba histolytica" Am J Hyg 5:371 1925) later also claimed to have cultivated pathogenic amebae and to have produced lesions in kittens with culture material. They were unable however with their method to produce encystment The work of Cutler has been sharply criticized by C Dobell (*The Amoebae Living in Man* p 70) A summary of the whole problem of cultivation of amebae is to be found in Anderson Bostick and Johnstone (*op cit*, pp 346 ff)

17 KARTULIS Gehirnabscesse nach dysenterischen Leberabscessen Centralbl f Bakt 37:527 1904

Kartulis reviews the meager literature on brain abscess occurring in association with dysentery and reports two cases of his own in which he found amebae both in the pus and in sections of the wall The subject is reviewed in detail by J A Orbison N Reeves C L Leedham and J M Blumberg "Amebic brain abscess review of the literature and report of five additional cases" Medicine 30:247 1951 This article has a bibliography of 82 titles

18 ROGERS Leonard The prevention and treatment of amoebic abscess of the liver Philippine J Sc 5B 219 1910

Rogers was the first to insist on the value of ipecac in the treatment of amebic hepatitis and abscess of the liver He points out that 86 per cent of a large series of liver abscesses were sterile as far as bacteria were concerned although in a few cases "numerous cocci and bacteria are found" "Lastly I would urge that every patient operated on for amoebic-liver abscess should be given a course of full doses of ipecacuanha as soon as possible with the view to healing the ulcers in the large bowel which have originated the hepatic trouble and are often latent and give rise to no symptoms"

19 ROGERS Leonard The rapid cure of amoebic dysentery and hepatitis by hypodermic injections of soluble salts of emetine Brit M J 1 1424 1912

Rogers briefly tells the story of ipecac in the history of medicine "The Brazilian root was first brought to Europe by Piso in 1658 and was successfully used by Helvetius in the treatment of Louis XIV and sold as a secret remedy to the French Government Turning, however to emetine Magendie and Pelletier ("Sur l émétine et sur les trois espèces d ipecacuanha" J gén de méd 59 223 1817) extracted an alkaloid from various types of ipecac the ligneous internal part of brown ipecac psycotria emetica contained for example 1 15 parts of "emetine" This material taken by mouth in 1 or 2 gm doses produced vomiting just as did ipecac Six to 12 gm killed a dog Finally the authors advised giving emetine in a sort of camomile tea in which "it is agreeable even to infants" The academy approved the report and thought "emetine" worthy of further clinical study although no results were reported in tropical dysentery H B Paul and A J Cownley ("The chemistry of ipecacuanha" Pharm J & Tr 53 [3d ser Vol 24] 61 1893) showed that the "emetine of earlier workers was really a mixture of several alkaloids It was many years later before E B Vedder ("A preliminary account of some experiments undertaken to test the efficacy of the ipecac treatment of dysentery" Bull Manila M Soc 3 48 1911) using cultures of non pathogenic amebae showed that both ipecac and emetine killed the organisms in the test tube Some preparations of emetine were effective in dilutions of 1 200 000 Vedder concluded "I would state my belief that the ipecac treatment of dysentery caused by protozoa should not on light grounds be set aside in favor of any other but that in using this treatment great care should be taken to make sure that the dysentery is truly caused by protozoa and is not bacillary and also to obtain an ipecac that is shown by critical analysis to contain its proper amount of emetin and when this is not possible to insist upon obtaining the Brazil root It is to Rogers, however, that

credit clearly goes for introducing the use of hypodermic injections of emetine in the treatment of amebiasis Three brilliantly successful cases are reported Rogers ("Further experience of the specific curative action in amoebic disease of hypodermic injections of soluble salts of emetine," Brit M J 2 405 1912) soon reported twelve further cases of various types of amebic dysentery and liver abscess cured by emetine "We have then in my method of the sub cutaneous injection of soluble salts of emetine a specific treatment of amoebic hepatitis and amoebic dysentery which is so rapidly beneficial in the latter as to be also of great diagnostic value between that and other causes of the passage of blood and mucus in the stools Yet strange to say this remarkable remedy—probably the most specific in the whole range of medicine not excluding quinine and salvarsan—has for long been thrown away by those who pinned their faith on ipecacuanha sine emetina "

This paper really opened the modern era of chemotherapy of amebiasis like similar efforts in other fields it was destined to be to some extent a disappoint ment since it was soon discovered that emetine was often inadequate to extir pate fully the infection so that relapses were prone to occur Rogers also devotes a chapter in his book (*op cit* p 117) to ipecac and emetine in amebic dysen tery

Emetine was soon combined with iodine and bismuth (E B I emetine bis muthous iodide) and was first tried on man in 1916 by G C Low and C Dobell ("Three cases of Entamoeba histolytica infection treated with emetine bismuth iodide" Lancet 2 319 1916 see also G C Low "Emetine bismuth iodide in amoebic dysentery amoebic hepatitis and general amoebiasis" Lancet, 1 482 1917) It seemed more effective than emetine in eradicating cysts and in treating the chronic tissue stages of the disease and is still widely used in England

20 WALKER E L and SELLARDS A W Experimental amoebic dysen tery Philippine J Sc ser B 8 253 1913

Walker and Sellards set about to prove that amebae really were the cause of "amebic dysentery by reproducing the disease experimentally The results of these elaborate investigations are quite clear First Walker re emphasizes the necessity in practice of distinguishing the harmless *E coli* from the pathogenic *E histolytica* in the stools of patients The differential features of both the motile stage and the encysted stage are clearly listed in tabular form Volunteers were then fed cysts of the various strains Those who ingested E *coli* developed no disease whereas dysentery was produced in some of those who received *histolytical* cysts Furthermore many of these who did not develop clinical dysentery became carriers Walker and Sellards drew the important final conclusion that *E histolytica* was to all intents and purposes the sole cause of amebic dysentery and that therefore exact diagnosis was of the utmost importance They also emphasized that vegetative forms did not survive outside the body but that cysts were the important element in transmission of the disease Consequently the recognition of "carriers" of cysts was the key to intelligent public health preventive measures

As to treatment this important statement is made "The evidence points to the conclusion that the ordinary routine treatment with ipecac while efficient

in relieving attacks of dysentery and in causing the entamoeba to disappear temporarily from the stools frequently does not kill all of the entamoeba in the intestine consequently the patient is liable to a relapse of the dysentery"

21 SELLARDS A W and BAETJER W A The propagation of amoebic dysentery in animals and the recognition and reproduction in animals of atypical forms of the disease Am J Trop Med 2 231 1914

Sellards and Baetjer summarize their work on experimental amebic dysentery Employing the device of injecting the stools containing amebae from acute attacks of dysentery directly into the cecum of kittens they succeeded in producing amebic infection in nearly 100 per cent of the animals and in propagating the disease through eleven generations They produced acute fatal infections chronic infections with relapses and liver abscess and carriers They succeeded in increasing the virulence of the infection on repeated passages in contrast to the usual reports of attenuation Their work was of great importance insofar as Sellards and Baetjer developed a valuable experimental tool. H H Dale and C Dobell ("Experiments on the therapeutics of amoebic dysentery" J Pharmacol & Exper Therap 10 399 1917) established amebic dysentery by injecting material high into the colon through a glass nozzle They studied the effect of emetine on the experimental disease "Experimental dysentery in kittens was refractory to all kinds of treatment Neither the ipecacuanha alkaloids nor other substances having a powerful action on the amoebae in vitro could cure the infection or definitely modify its course" They therefore concluded that the theory of direct amebicidal action of emetine on the parasite was no longer tenable

In this connection one should not fail to mention the early systematic experiments on production of amebic dysentery in cats and kittens by F Kovács ("Beobachtungen und Versuche uber die sogenannte Amoebendysenterie" Ztschr f Heilk 13 509 1892) Incidentally his paper opens with one of the best reviews we have found of early work on the relation of amebae to dysentery

22 LEVY R L and ROWNTREE L G On the toxicity of various commercial preparations of emetine hydrochloride Arch Int Med 17 420 1916

In this important study the writers review the earlier literature and report several new cases of emetine poisoning Bowel and cardiac disturbances are described In animals they were able to produce ventricular fibrillation confirmed by the electrocardiograph They point out that toxic effects are largely the result of overdosage and that intravenous injection is usually unnecessary "One third of a gram three times a day for a week or ten days is usually a safe dosage" S Dack and R E Molostok ("Cardiac manifestations of toxic action of emetine hydrochloride in amebic dysentery" Arch Int Med 79 228 1947) have recently reviewed the subject as have G Klatstein and H Friedman ("Emetine toxicity in man" Ann Int Med 28 892 1948) The latter paper contains a comprehensive bibliography

Earlier papers of interest on ipecac poisoning are those of D Duckworth ("Observations upon the action of ipecacuanha and its alkaloid emetia" St

Barts Hosp Rep, 5:218 1869) who reviews previous experiments and reports observations on the gross effects of the drug in animals and of von Podwyssotzki ("Beiträge zur Kentniss des Emetins" Arch f exper Path u Pharmakol 11 231 1879) who made a systematic study of the drug using classical pharmacological technique His description of the action on the exposed frog heart with progressive irregularity until "finally the entire heart remains in an exquisite paralytic diastolic standstill" is very vivid

23 THOMSON J G Human entamoebiasis in temperate zones J State Med 33 563 1925

Musgrave (Ref 16) had already introduced the idea of "amoebiasis" and of carriers" The concept rapidly gained acceptance and it was soon found that amebae could be found frequently in apparently healthy persons outside the "tropics" Thomson gives an elaborate table of reports on the incidence of amebae in people some of whom had never been out of the temperate zone "It can be said that an amoebic infection is in the majority of instances an insidious disease of such a mild character as to pass unnoticed by the patient, and while it may be true that a contact carrier may remain apparently healthy all his life there is no method of accurately telling what pathological lesions are produced except in the post mortem room" W M James ("Diagnosis of intestinal amebiasis" J A M A 89 1469 1927) points out the difficulty of accurate diagnosis of intestinal infection with *histolytica* and also gives figures on incidence C A Kofoid ("Statistical summary of persons examined for protozoa and worms etc *Twenty ninth Biannual Report of the State Board of Health of California* [Sacramento 1926] p 93) gives the widely quoted figure of 13 1 per cent incidence of *Endamoeba dysenteriae* among some sixteen hundred "healthy" people J F Kessel and V R Mason ("Protozoan infection of the human bowel" J A M A. 94 1 1930) arrived at a similar figure in the Los Angeles County Hospital An especially valuable review of this whole subject is that of W C Boeck "Survey of 8 029 persons in the United States for intestinal parasites with especial reference to amoebic dysentery among returned soldiers" Hyg Lab Bull No 133 (Washington 1923) p 1 At any rate it is clear that there exists a widespread incidence of bowel infestation with these parasites a far cry from the original view that there existed only vegetative forms associated with acute dysentery

24 REED A C ANDERSON H H DAVID N A and LEAKE C D *Carbarsone in the treatment of amebiasis* J A M A 98 189 1932

For a decade after its introduction by Rogers (Ref 19) emetine had no serious contenders in the field of therapy of amebiasis although it was soon realized that relapses were common and that complete cure was effected in only 28–70 per cent of the cases (Ref 20) Serious toxic effects also turned out to be not uncommon (Ref 22) Attention was therefore soon turned to other drugs which might be useful and in subsequent years innumerable preparations have been tried which cannot all be reviewed here For the earlier literature the reader is referred to the review by O Willner "Remedies recently introduced in the therapy of amoebiasis" Medicine 6 341 1927 and to the excellent paper by C D Leake "Chemotherapy of amebiasis" J A M A 98 195 1932 Later

reviews are those of G A Martin *et al* "Comparative efficacy of amebicides and antibiotics in acute amebic dysentery" J A M A **151**:1055 1953 and of H E Hamilton "Treatment of amoebiasis" Arch Int Med **91** 612 1954

Carbarsone (4 carbamino-phenyl arsonic acid) is one of the few earlier drugs which have stood the test of time Reed and his associates report a careful clinical study with good results "More closely than any other drug now exploited does carbarsone meet the requirements of an ideal antiamebic agent It is clinically nontoxic in effective doses it may conveniently be administered orally without interference with the patient s usual routine it has no untoward side actions and it is comparatively cheap"

Hamilton s review (*op cit*) is especially helpful in bringing out the confused state of the subject at present He points out that with single drugs relapse rates have been disappointingly high and that the tendency now is to use two or three agents in combination or succession He notes that the drugs effective in clearing the bowel infection—bowel phase—must be distinguished from those more effective against the parasites deep in the tissues—tissue phase The drugs primarily effective against the tissue phase are chloroquine emetine and quinacrine Of these chloroquine (see N J Conan "Chloroquine in amebiasis" Am J Trop Med **28** 107 1948) seems at present most safe and efficient Hamilton also lists the drugs effective against the bowel phase of which di iodohydroxyquinoline is quite satisfactory The point of all this however is clear There is as yet no entirely satisfactory drug nor is there agreement among various observers as to which is the best The subject is still in a state of flux

25 SCHWARTZWELDER J C Experimental studies on *Endamoeba histolytica* in the dog Am J Hyg **29**:89 1939

Much work has been done in the attempt to define the mode of infection by the parasite Schwartzwelder reviews the literature and reports his own observations on excystation in dogs which occurred both in the ileum and in the large intestine "The time required to bring about the process varied from 1 5 to 4 5 hours following oral inoculation with cysts" The details of invasion of the bowel by the excysted amebae are reviewed and discussed by W M James "Human amoebiasis due to infection with *Entamoeba histolytica*" Ann Trop Med **22** 201 1928

26 McHARDY G and FRYE W W Antibiotics in management of amebiasis J A M A **154** 646 1954

It was inevitable with the advent of the antibiotics that they should be tried in amebiasis and there are numerous papers reporting trials with one or another agent This work is reviewed by McHardy and Frye who concluded that of the broad spectrum antibiotics oxytetracycline (Terramycin) is the drug of choice since in the literature only 8 5 per cent of relapses were reported among 435 treated cases "Hepatitis hepatic abscess and other extracolonic amebic involvements are not benefitted by treatment with the antibiotics evaluated"

27 SPICKNALL C G and PIERCE E C II Amoebic granuloma New England J Med **250**:1055 1954

The first description of amebic tumors" is usually attributed to Kartulis (*Dysenterie* [Vienna Alfred Holder 1896] p 60) but an inspection of his

article does not make it clear that he saw localized tumors which could be for example confused with cancer H Gunn and N J Howard ("Amebic granuloma of the large bowel" J A M A 97:166 1931) review the early references and introduce the term "amebic granuloma" which is now widely accepted "The pathologic process consists in persistence of an isolated chronic ulcer with progressive erosion of the wall of the bowel In response to the amebic ulceration and secondary infection large amounts of edematous fibrous granulation tissue appear These granulomas may be easily mistaken for carcinoma for they give symptoms physical signs and radiologic appearances that may be identical with those produced by carcinoma" Spicknall and Pierce however give a definitive review of the subject with a bibliography of 125 titles The main point is the frequency of a lesion in the cecal region and the likelihood of its being confused with acute appendicitis abscess or tumor

Section 21

INFLUENZA

Blood count in influenza	Ref 6
Carriers of virus	Ref 23
Clinical features	Refs 1 5 19
Cultivation of virus	Refs 9 17
Epidemiology	Refs 24 25
Etiology viral	Refs 9 10 11 13
General	Refs 4 25
Immunology	Refs 12 14
The influenza bacillus	Refs 2 3 5
Pathology	Refs 7 11 16
Red cell agglutination by virus	Refs 20 21
Size and characterization of virus	Ref 22
Transmission	Refs 8 9 10 11 13
Types of virus	Refs 14 18 21
Vaccination against influenza	Refs 14 15

Section 21

INFLUENZA

THE bibliography of influenza presents an extremely difficult problem Before the pandemic of 1918 there was great confusion on the clinical side since the "discovery" of the virus (1933), a vast literature has accumulated dealing with the complexities of transmission of immunity of multiple strains of the constitution of the virus and many other phases of the subject A long list could readily be compiled for example of articles that deal only with the size of influenza virus particles In a bibliography of this sort therefore designed primarily for students and clinicians, it has been necessary to confine ourselves mainly to the first or to early articles on each phase of the subject this procedure may be regarded as an excuse for incompleteness but the purpose has been to induct our readers into the subject as a whole rather than to pinpoint special aspects

Comprehensive bibliographies are to be found in the following works

HIRSCH AUGUST *Handbook of Geographical and Historical Pathology* I 41 London New Sydenham Society 1883

LEICHTENSTERN O "Influenza" In NOTHNAGEL, *Specielle Pathologie und Therapie* Vol 4, Part I Vienna Alfred Holder 1896

JORDAN EDWIN O *Epidemic Influenza A Survey* Chicago American Medical Association 1927

THOMSON D and THOMSON R "Influenza" In *Annals of the Pickett Thomson Research Laboratory* Vol 10 Baltimore Williams & Wilkins Co 1934

For references to the modern experimental study of influenza see the article by Horsfall in RIVERS THOMAS M *Viral and Rickettsial Infections of Man* p 382 Philadelphia J B Lippincott Co 1952

It is not our purpose to try to disentangle the early vague and uncertain accounts of epidemics of respiratory disease The occurrence however of sharp and widespread outbreaks of a disorder of brief duration featured by sudden onset great prostration and "catarrhal" symptoms makes it probable that many of these actually were influenza Lists of such epidemics or pandemics going back many centuries are given in the monographs by Hirsch and by Leichtenstern and firsthand descriptions may be read in Theophilus Thompson's compilation, *Annals of Influenza etc* (London Sydenham Society 1852)

The origin of the term "influenza" is obscure Leichtenstern—later often quoted—states that the word comes from the Italian *influenza di freddo* or the influence of cold. In general however the word "influence" in this sense has been used more with reference to the stars or the planets than to atmospheric effects Dr Thomas Glass of Exeter for example is quoted in the *Annals of Influenza* (p 101) as saying "Physicians imputed the Epidemic Catarrhous Semi Pestilential Fever to the influence of the stars whence the Italians gave it the name of Influenza" Furthermore in many of the earlier accounts the word seems to be used not as a specific name but as a general designation—as one spoke of a "flux" or of a "fever" Thus Dr Molyneux in 1694 (*Annals of Influenza* p 24) says "So general did this influenza rage that few or none

escaped " By the end of the eighteenth century however the term "influenza" was used in much the same sense as today to designate a distinct disorder

In the pandemic of 1918–19 the violent disease had such fixed clinical char acteristics as to be easily recognized Since then however most outbreaks have not been very severe and it has often been impossible to differentiate on clini cal grounds alone mild "influenza" from a severe "common cold" or from other minor respiratory infections This difficulty has greatly complicated studies of the etiology and ecology of influenza

1 PARKES Edmund A Influenza *in* A system of medicine ed J Russell Reynolds 1:28 2d ed London Macmillan & Co 1870

Although there are innumerable clinical descriptions of influenza in the older literature they usually consist of a catalogue of various symptoms without any real appreciation of a specific disease entity The occurrence in epidemics or pandemics of fever great prostration respiratory and other complaints is em phasized in varying degree Whether or not Charles Lamb for example was suffering from postinfluenzal asthenia when he wrote the following in 1824 (*The Letters of Charles and Mary Lamb* ed E V Lucas [London J M Dent & Sons 1935] 2 413) we leave to the reader to guess "Do you know what it is to succumb under an insurmountable day mare—an indisposition to do any thing, or to be anything—a total deadness and distaste—a suspension of vitality—an indifference to locality—a numb soporifical good for nothingness—did you ever have a very bad cold with a total irresolution to submit to water gruel processes?"

The first clinical description we have found which seems to show any real understanding of the disease is that of Parkes "The symptoms of Influenza are compounded of two conditions—a general fever of determinate duration and a marked and evidently specific affection of the mucous membrane of the nose mouth, throat and respiratory tract which has also a determinate course" The symptoms 'last for four or five days usually—sometimes they continue ten or twelve days but this is generally when pneumonic complication supervenes" "A punctiform redness of the mucous membrane of the palate something like the eruption of measles has been lately described by Tigri [A Tigri "Sul grippe" Ann Univ de med Milano 102 667 1867] and considered to be pathognomonic." Parkes sensed that influenza was not simply an indefinite "catarrhal disease but a disorder of fixed and specific characteristics

2 PFEIFFER R Vorlaufige Mittheilungen uber die Erreger der Influenza Deutsche med Wchschr 18 28 1892

Although it is now known that the bacillus of Pfeiffer is not the cause of influ enza its etiological role was considered to be settled for so many years that the important articles dealing with the subject should be included in the bibliogra phy It must be remembered that Pfeiffer was a topflight bacteriologist He was a colleague and friend of Robert Koch Flugge and Kolle He did out standing work in cholera typhoid fever and other diseases He worked in one of the best-equipped institutions in the world for the study of infectious dis eases His integrity was unquestioned, and his work had to be taken seriously

In this brief communication Pfeiffer reports the results of his studies in thirty-one cases of influenza six with autopsy In every case he found in the

bronchial secretions a "certain bacillus "In uncomplicated cases of influenza these rods were present in pure culture and usually in tremendous numbers" Furthermore they were found only in influenza patients He describes the morphology of the organism, the staining reactions (Gram negative) and the difficulties of artificial culture This convincing array of evidence was amplified in the next paper

3 PFEIFFER R Die Aetiologie der Influenza Ztschr f Hyg u Infektionskr **13**:357 1893

In this comprehensive paper Pfeiffer amplifies his brief preliminary report (Ref 2) The constant finding of the influenza bacillus" in cases of influenza is reiterated and the necessity of a hemoglobin containing medium for successful growth is pointed out Inoculation experiments in monkeys are interpreted much more conservatively than those of Blake and Cecil nearly thirty years later (Ref 5) The paper is a model of careful work by an experienced investigator and as one reads it, it is easy to see why the Pfeiffer bacillus was almost universally accepted as the cause of influenza until the pandemic of 1918 Even then and for reasons identical with Pfeiffers many experienced students of infectious disease still believed firmly in the etiological role of the Pfeiffer bacillus (see E L Opie J Small F G Blake and T M Rivers, *Epidemic Respiratory Disease* [St Louis C V Mosby Co 1921])

However Pfeiffer probably confused the situation by regarding hemoglobinophilic bacteria isolated from diseases other than influenza as pseudo influenza bacilli

4 LEICHTENSTERN O Influenza *in* Nothnagel Specielle Pathologie und Therapie, Vol 4, Part I Vienna Alfred Holder 1896

No student of influenza can afford not to be familiar with this classical monograph Based largely on the pandemic of 1890 it is definitive to date and takes up in great detail every aspect of the subject

5 BLOOMFIELD Arthur and HARROP George A Jr Clinical observations on epidemic influenza *Bull Johns Hopkins Hosp* *30 1 1919*

During the pandemic of 1918 Bloomfield and Harrop were able to study carefully the clinical phenomena in a closed group of young people They were struck by the fact that epidemic influenza was a disease of highly fixed characteristics like measles chickenpox or other disorders of probable viral origin They emphasized (*a*) typical onset with a group of constitutional symptoms (*b*) a striking erythema of the head and upper body (*c*) a typical enanthem (*d*) diffuse inflammation of the upper air passages (*e*) fever of determinate duration (*f*) leucopenia and (*g*) a remarkable tendency to secondary bacterial infection in the lungs To this might be added a curious and unexplained profound prostration *quite out of proportion to what is usually seen in other* infections

Although at the time the influenza bacillus was generally accepted in America as the cause of the 1918 pandemic (Ref 3) Bloomfield and Harrop could not believe that an organism so ubiquitously found as a saprophyte in interepidemic times could suddenly cause a specific disease of such highly fixed characteristics Furthermore in the Baltimore outbreak as well as elsewhere

influenza bacilli frequently were not isolated (S E Howard "Bacteriological findings in epidemic influenza" Bull Johns Hopkins Hosp 30 13 1919) After casting doubt on the role of the Pfeiffer bacillus as the primary cause of influenza the writers stated "It is probable that the actual virus is as yet un identified" a prediction which was verified in 1933 (Refs 9 10) At about the same time the case against the influenza bacillus was clearly stated by F T Lord A Scott and R N Nye (Relation of the influenza bacillus to the recent epidemic of influenza" J.A M.A 72:188 1919) On the other hand as late as 1920 prominent workers such as F G Blake and R L Cecil ("The production of an acute respiratory disease in monkeys by inoculation with Bacillus influenzae" J A M A 74 170 1920) believed that they had produced influen za in monkeys by buccal or nasal instillation of cultures of *B influenzae* Some of their conclusions were "The disease appears to be identical with influenza in man" "It seems reasonable to infer that B influenzae is the specific cause of influenza" All this will give the reader some idea of the active dispute as to etiology which followed the 1918 pandemic The extensive contemporary liter ature is reviewed by Jordan (*op cit*)

Bloomfield (Bull Johns Hopkins Hosp 33 172 1922) later discussed the general significance of the influenza bacilli He analyzed the evidence that these organisms which were not present in over 20 per cent of normal throats before the pandemic of 1918 became widespread during and for 2 years after the pan demic but by 1921 were again found in less than 20 per cent of healthy people Since the influenza bacilli isolated from patients were found to be a group of immunologically distinct varieties (see W H Park J.A M.A 83 318 1919) and since they were frequently obtained from the respiratory passages of patients with diseases other than influenza such as measles (A W Sellards and E Sturm "The occurrence of the Pfeiffer bacillus in measles" Bull Johns Hopkins Hosp 30 331 1919) it appeared that certain disorders especially influenza promoted an associated infection or infestation with the influenza bacillus group but that these organisms were not the cause of the primary dis ease An analogous situation was worked out by R E Shope ("The influenzas of swine and man" Medicine 15 453 1936) who showed that in swine influ enza there was an association of a virus (the primary cause) with swine influen za bacilli

At any rate it seems clear that pandemic influenza in some way promotes great prevalence of the Pfeiffer bacillus in the respiratory passages of the gen eral population

6 DOUGLAS Beverly The reaction of the leucocytes in epidemic influenza Bull Johns Hopkins Hosp 30 338 1919

Careful total and differential leukocyte counts were made during the pandemic of 1918 and the frequency of marked leukopenia was pointed out Fifty per cent of Douglas group had leukocyte counts of under 5 000 Ten per cent had counts of less than 3 000 In a comparable group of mild non pandemic cases studied by Doull and Bahlke (Ref 19) only 23 2 per cent had counts under 5 000

Douglas paper seems to be the first systematic study of this important diag nostic sign

7 MACCALLUM W G The pathology of the pneumonia following influenza J A M A 72:720 1919

During and after the pandemic of 1918–19 an extensive and confusing literature on the pathological anatomy of influenza accumulated The cause of influenza being as yet unknown it was impossible to distinguish the fundamental lesions of the disease from those produced by the secondary invaders so abundant and so invariably present in the respiratory tract We believe that credit is due to MacCallum for sensing a basic lesion even though vaguely apart from the secondary bacterial bronchopneumonias "But now it appears that streptococci and influenza bacilli may in precisely similar ways be governed it seems unnecessary to ascribe one type of lesion to the streptococcus and another to the influenza bacillus MacCallum described quite distinctly the interstitial changes in the lung now known to be characteristic of virus pneumonitis of various kinds The whole subject is elaborated and extensively pictured in his monographs ("The pathology of the pneumonia in the United States Army camps during the winter of 1917–18" Johns Hopkins Hosp Rep Vol. 20, Fasc 1 [Baltimore 1920] and "Pathological anatomy of pneumonia associated with influenza" *ibid* Fasc 2 [1921]) Another outstanding pathologist reviewed the subject later (E L Opie "The pathological anatomy of influenza" Arch Path & Lab Med 5 285 1928) but it was necessary to wait for the experimental production of influenza in animals (Refs 10 11) to define the uncomplicated lesions No accounts can be found of fatal influenza uncomplicated by secondary lesions of bacterial origin

8 ROSENAU Milton J Experiments to determine mode of spread of influenza J A M A 73 311 1919

The question of how influenza spreads through the population had always been under active dispute In the early days authorities divided themselves into contagionists" and "non contagionists The former thought that an infective agent was transmitted from case to contact the latter believed rather that some "miasm was widely diffused probably through the air so that large groups were simultaneously attacked A Biermer for example an astute observer whose account of influenza as early as 1854 is a masterpiece (in R Virchow [ed] *Handbuch der speciellen Pathologie und Therapie* [Erlangen Ferdinand Enke 1854] 5 592) argued against contagion He was impressed by the frequency with which people living in intimate contact with patients failed to acquire the disease and he thought that outbreaks of influenza were often too explosive to be explained by person to-person contact After the 1890 pandemic when everyone believed the Pfeiffer bacillus was the cause of influenza it was assumed that the disease was spread by rapid dissemination of these organisms However there were still many contradictions in the observed epidemiological facts so Rosenau during the 1918 pandemic planned the rigorous tests described in this paper Even though the results were negative they are of the greatest importance The procedure was as follows The donors were patients in the first to third day of typical epidemic influenza The volunteers were healthy young men who as far as could be told had not had influenza There was no reason to think they were all immune Nasal washings from the donors were sprayed and instilled into the throats of the volunteers Swabs from the donors

were rubbed directly over the pharynges of the volunteers When these meth ods failed to produce any disease the following drastic experiment was carried out

The volunteer was led up to the bedside of the patient he was introduced He sat down alongside the bed of the patient They shook hands and by in structions he got as close as he conveniently could and they talked for five minutes At the end of the five minutes the patient breathed out as hard as he could while the volunteer muzzle to muzzle (in accordance with his instructions about 2 inches between the two) received this expired breath and at the same time was breathing in as the patient breathed out This they repeated five times and they did it fairly faithfully in almost all the instances

After they had done this for five times the patient coughed directly into the face of the volunteer face to face five different times After one volunteer had had this sort of contact with the patient talking and chatting and shaking hands with him for five minutes and receiving his breath five times and then his cough five times directly in his face he moved to the next patient whom he had selected and repeated this and so on until this volunteer had had that sort of contact with ten different cases of influenza in different stages of the disease mostly fresh cases none of them more than 3 days old

This experiment was repeated at various times and in various locations In no case was an illness in any way resembling influenza produced The full protocols are given in Bulletin No 123 from the Hygienic Laboratory of the United States Public Health Service Washington February 1921 The importance of these negative experiments cannot be overlooked why others (Ref 9) were able to transmit mild interepidemic influenza by much less drastic methods remains a puzzle

The modern philosophy of transmission is discussed in Reference 25

9 DOCHEZ A R MILLS K. C and KNEELAND Yale Jr Studies of the etiology of influenza Proc Soc Exper Biol. & Med 30 1017 1933

Although opinion generally favored a bacterial agent as the cause of influenza at the time of the 1918 pandemic some workers were already investigating the question of a viral etiology Various "rudimentary transmission experiments presently to be discussed suffered from uncertainty as to the identity of the disease which was produced usually a mild general reaction often without any respiratory symptoms In interepidemic times it was also hard to be sure of the identity of the donor disease H Selter ("Zur Aetiologie der Influenza" Deutsche med Wchnschr 44 932 1918) sprayed the throats of two volun teers with a filtrate of material obtained by throat swabs A mild illness with constitutional symptoms slight fever but little in the way of respiratory symptoms resulted The author however thought his observations supported a virus etiology Similarly C Nicolle and C Lebailly (Recherches expérimentales sur la grippe Ann Inst. Pasteur 33 395 1919) thought that they had produced an influenza like disorder in monkeys by nasal instillation and subconjunctival injection of filtrate from throat washings of influenza patients Two human volun teers were considered to develop influenza after subcutaneous injection of fil trate T Yamanouchi and his associates in a brief note from Japan ('The in fecting agent in influenza Lancet 1 971 1919) believed that they had pro duced influenza with sputum filtrates instilled into the throat and also by sub-

cutaneous injection Filtrates of blood from influenza patients instilled into the noses and throats of human volunteers were also said to produce influenza After a preliminary note ("A filterable virus as the cause of the early stage of the present epidemic of influenza," Brit M J 2 645 1918) H Gibson F Bowman and J Connor issued a lengthy report ("Medical Research Committee Special Reports" No 36 [London 1919]) on transmission experiments with filtrates of throat secretions and blood from influenza cases to monkeys rabbits guinea pigs and mice—work which later observers (Ref 10) were unable to confirm More convincing are the careful observations of P Long E Bliss and H Carpenter ("Etiology of influenza" J A M A 97 1122, 1931), who produced a disorder "characterized by fever prostration and leukopenia" in monkeys by pharyngeal inoculation of filtrates of nasopharyngeal washings from cases of influenza All this work is however, difficult to interpret, especially in the light of the extensive negative transmission experiments of Rosenau (Ref 8) Furthermore monkeys have not been found to develop clinical symptoms from inoculation of influenza virus nor have animals or man come down when inoculated by routes other than the respiratory tract even though parenteral injection has led to the development of immune bodies (Ref 12)

The work of Dochez and his associates was much more decisive They clearly produced a respiratory disease in a volunteer inoculated intranasally with filtrates of throat washings from a case of influenza They also succeeded in propagating an infectious agent in chick embryo medium (see Dochez Mills and Kneeland Study of the virus of the common cold and its cultivation in tissue medium" Proc Soc Exper Biol & Med 28 513 1931) through many generations after which the material again produced respiratory infection in man Dochez found it difficult to distinguish possible influenza virus from that of the common cold In another paper ("Studies on the virus of influenza," J Exper Med. 63 581 1936) the same writers amplified their work Meanwhile T Francis Jr and T P Magill (Cultivation of human influenza virus in an artificial medium Science 82 353 1935) reported more extensive cultivation experiments in chick embryo medium in which virus from mouse lung propagated for many generations was then capable of producing disease in both mice and ferrets

10 SMITH Wilson ANDREWES C H and LAIDLAW P P A virus obtained from influenza patients Lancet, 2 66 1933

Although Dochez's paper (Ref 9) published a few weeks before that of Smith Andrewes and Laidlaw gives convincing evidence of isolation of a filterable virus from patients with influenza it was with the work of the latter investigators that the modern study of influenza may really be said to have begun This paper is therefore an important landmark Throat washings from cases of influenza seen during the 1933 epidemic in England were inoculated into various animals without success until ferrets were used The original animals received the material both intranasally and subcutaneously The experimental disease had an incubation period of 1 or 2 days and was featured by fever lethargy weakness and catarrhal symptoms although there was a good deal of variation Sections of the nasal mucosa of the ferrets showed acute inflammation often with necrosis of the epithelium (see also Ref 16) The dis

ease was transmitted serially to other ferrets by contact or by nasal instillation of filtrates of an emulsion of the nasal mucosa No route of infection other than the nasal proved effective "The infectivity of the filtrates coupled with the fact that we failed to grow anything from the filtrate—has convinced us we are dealing with a true virus disease" Ferrets recovered from the disease were immune to subsequent infection with the same strain of virus and the serum of ferrets recovered from the disease neutralized emulsions of the virus Normal ferret serum had no such power Throat washings from healthy subjects and influenza convalescents produced no disease in ferrets nor did the secretions from a subject with a severe common cold Convalescent sera and some human sera in general contained neutralizing bodies against the ferret disease

This thorough work by experts in the field was immediately acclaimed, and a vast amount of investigation followed which confirmed the writers findings We cannot catalogue the huge literature which has accumulated except for the papers that bring out something fundamentally new It was Smith Andrewes and Laidlaw s report, however which led to universal agreement that influenza was a disease of viral origin The confirmatory but independent work of Francis ("Transmission of influenza by a filterable virus" Science 80 457 1934) is especially to be mentioned.

11 ANDREWES C H LAIDLAW P P and SMITH Wilson The susceptibility of mice to the viruses of human and swine influenza Lancet 2 859 1934

The work described in the previous paper (Ref 10) was carried further by similar methods and it was found that a disease transmissible in series could be produced in mice lightly anesthetized by nasal instillation of material from the lungs of infected ferrets In the mouse in contrast to the ferret the principal lesion was in the lung—an area of consolidation "not unlike some of those encountered in influenzal pneumonia in man" However I Brightman (Am J Dis Child 52 78 1936) later described lesions in the lungs of ferrets inoculated with influenza washings which conform to the interstitial type of pneumonitis commonly produced by various viruses The use of mice has been an important aid in the study of influenza virus

12 FRANCIS Thomas Jr and MAGILL T P Immunological studies with the virus of influenza J Exper Med 62:505 1935

Francis and Magill made the important observation that subcutaneous inoculation of rabbits and mice with influenza virus did not cause clinical disease but produced active immunity with the appearance of antibodies in the blood *Studies of this sort later furnished the basis for attempts actively to immunize human beings (Ref 15)*

During the next few years innumerable papers appeared on various phases of immunity to influenza

13 SMITH Wilson and STUART HARRIS C H Influenza infection of man from the ferret Lancet 2 121 1936

An important step in the characterization of influenza virus was of course proof that the experimental disease could be transmitted back to man In this paper there is fairly convincing evidence that "S H" contracted influenza from

a ferret sick with passage virus Immunological studies demonstrating increase in antibodies in the patient are presented

Francis and his associates later (Am J Pub Health 34 317 1944) reported on the production of influenza in man with type B virus which had been passed through eggs and ferrets for many generations

14 FRANCIS Thomas Jr and MAGILL, T P The incidence of neutralizing antibodies for human influenza virus in the serum of human individuals of different ages J Exper Med 63 665 1936

The writers found that about 50 per cent of the sera of individuals of various ages with no history of influenza contained sufficient antibody *after* the first year of life to furnish complete protection to mice These observations suggested of course a high degree of unrecognized infection with influenza virus The complexities of this subject were further analyzed by E Rickard E Lennette and F Horsfall (Comprehensive study of influenza in a rural community " Pub Health Rep 55:2146 1940) Antibody levels against influenza A virus were determined during a non epidemic interval among 1 101 persons from four to eighty five years of age Variations in titer in relation to many factors including history of infection resistance etc are discussed The same investigators with G Hirst carried the study further ("Correlation between neutralizing antibodies in serum against influenza viruses and susceptibility to influenza in man Pub Health Rep 56 1819 1941) and showed that the level of neutralizing bodies against the homologous type was important in determining susceptibility to influenza but there was no cross immunity between types A and B (Ref 18) A great many other papers which we cannot list deal with variations on this theme

15 FRANCIS Thomas Jr and MAGILL T P The antibody response of human subjects vaccinated with the virus of human influenza J Exper Med 65 251 1937

It had been shown (Refs 10 11) that infection of mice and ferrets took place only by the respiratory route However animals inoculated subcutaneously or intraperitoneally developed active resistance to infection by the respiratory route (Refs 10 12) Francis and Magill vaccinated human volunteers by the subcutaneous or intradermal routes with virus grown in tissue culture medium A "good titer of circulating antibodies effective against mouse passage virus developed The antibodies persisted for at least 5 months A preliminary note of this work appeared in 1936 ("Vaccination of human subjects with virus of human influenza Proc Soc Exper Biol & Med 33 604)

These experiments furnished the basis for the attempts at systematic vaccination against influenza which were later made J Stokes and his associates for example (Results of immunization by means of active virus of human influenza " J Clin Investigation 16 237 1937) working in a state colony in the presence of an oncoming epidemic of "influenza " found that among those vaccinated there was an incidence of 2 7 per cent of febrile cases as against 12 5 per cent among the controls

Although a large amount of work on the subject was subsequently done vaccination against influenza has never had wide success partly because immunity is short lived, partly because it is impossible to predict the character of the

strains which cause various outbreaks and partly because there are wide varia tions in antibody response of different individuals (Hirst Rickard Whitman and Horsfall "Antibody response of human beings following vaccination with influenza viruses" J Exper Med 75:495 1942) Early reports of clinical experiences are to be found in the American Journal of Hygiene for 1945 where the entire July number is devoted to the subject T Francis Jr J Salk, and their associates also made important observations ("Protective effect of vaccination against induced influenza" J Clin Investigation 24 536 1945 see also Ref 18)

16 FRANCIS Thomas Jr and STUART HARRIS C H Studies of the nasal histology of epidemic influenza in the ferret J Exper Med 68 789 1938

The writers made daily histological studies of the nasal mucosa of ferrets after instillation of influenza virus They found that by 48 hours complete destruction of the respiratory epithelium had occurred This was followed by deeper changes It required several weeks for the reparative processes to be complete Meanwhile M Straub (J Path & Bact 45:75 1937) reported on the microscopic changes in the lungs of mice infected with influenza virus The same pattern was disclosed namely "necrobiosis and fibrinoid necrosis of the epi thelium of the respiratory and terminal bronchioles leading to a state of com plete epithelial desquamation" It appears that the virus of influenza in the ex perimental animal and in the chick embryo (Ref 17) localizes specifically in the respiratory epithelium and is not to be found in other accessible areas or in the blood

If a similar lesion occurs in the deeper air passages in human influenza as seems highly probable many of the clinical features of the disease are ex plained, including the tendency to secondary infection because of the injured mucous membrane and the prolonged and distressing cough which so often follows the acute attack

17 BURNET F M Influenza virus infection of the chick embryo by the amniotic route Australian J Exper Biol & M Sc 18:353 1940

The use of chick embryo infection has become so essential in the study of in fluenza that this important paper should be mentioned The technique of egg inoculation is described It is pointed out that the lesions affect primarily the epithelial lining of the respiratory tract particularly within the developing lung which contains more virus than any other organ although large amounts are present in both amniotic and allantoic fluids (see also F M Burnet, "Influ enza virus infection of the chick embryo lung" Brit J Exper Path 21 147 1940) Hirst later ("Direct isolation of influenza virus in chick embryos" Proc Soc Exper Biol & Med 58 155 1945) found that, by adding penicillin to unfiltered throat washings they could be inoculated directly into the amniotic sac without the complication of bacterial infection Wilson Smith ("Cultivation of the virus of influenza" Brit J Exper Path 16:508 1935) seems however to have been the first to propagate influenza virus in the living chick embryo although no lesions were to be seen in the early passages The whole subject is reviewed by Burnet in *The Use of the Developing Egg in Virus Research* ("Medical Research Council Special Report Series No 220 [London 1936])

18 FRANCIS T Jr A new type of virus from epidemic influenza *Science* 92 405 1940

During the first few years of the experimental study of influenza (Ref 10) it was thought that there was only one type of virus Strains isolated in England in the United States in Puerto Rico and elsewhere were shown by immunological tests to be identical H Reimann and J Stokes ("Epidemic infection of respiratory tract in 1938–1939 a newly recognized entity Tr A Am Physicians 54 123 1939) and others had however, studied outbreaks of respiratory disease which resembled influenza, in which convalescent sera contained no neutralizing antibodies for the viruses previously isolated In 1940 Francis isolated from an outbreak in New York State an agent which produced the typical reactions of influenza in ferrets but which by all existing immunological criteria could not be the hitherto identified virus It turned out that it was another type of influenza virus immunologically quite distinct from the original strains Francis suggested that the new type be designated type B in contrast to the previously defined type A At about the same time Magill ("A virus from cases of influenza like upper respiratory infection," Proc. Soc Exper Biol & Med 45 162 1940) also reported recovery of a virus immunologically distinct from the standard PR_8 strain (A) The diseases produced by the two types were clinically indistinguishable In the same year Horsfall Lennette and Rickard (Lancet 2 413 1940) discussed the whole question of the terminology of respiratory viruses and suggested the probability that further immunologically unrelated strains would be discovered A Rasmussen J Stokes and J Smadel ("The army experience with influenza 1946–1947 II Laboratory aspects" Am J Hyg 47 142 1948) reported on influenza in the army during 1946–47 The so called Fort Monmouth strain of virus from this outbreak was definitely not influenza B and also had significant immunological differences from the usual strains of influenza A Standard influenza A vaccine failed to protect against infection with the F M strains (see also Ref 15) These reports illustrate the extreme complexity of the antigenic relations among various strains of influenza virus

Francis (Differentiation of influenza A and influenza B by complement fixation reaction" Proc Soc Exper Biol & Med 45 861 1940) was able to differentiate influenza viruses A and B by means of complement fixation W Smith ("The complement fixation reaction in influenza" Lancet 2 1256 1936) had already shown that infected mouse lungs could be used as antigen for complement fixation and Lennette and Horsfall ("Studies on epidemic influenza virus the nature and properties of the complement fixing antigen" J Exper Med 72 233 1940) were later to show that influenza virus elaborates a soluble antigen

19 STUART HARRIS C H SMITH W and ANDREWES C H The influenza epidemic of January–March 1939 *Lancet* 1 205 1940

The clinical definition of influenza in relation to the type of virus is of course of great importance Numerous papers have dealt with this subject which is still in a confused state because of the difficulty in clinical identification of mild respiratory infections This paper and that of F Horsfall R Hahn and E Rickard ("Four recent influenza epidemics an experimental study" J Clin

Investigation 19:379 1940) may be mentioned as examples of thorough study of mild interpandemic influenza from both the clinical and the viral standpoint J Doull and A Bahlke ("Epidemic influenza a comparison of clinical observations in a major and a minor epidemic" Am J Hyg 17:562, 1933) made a careful comparison of the clinical features of a minor epidemic (1928–29) occurring in the institution where pandemic influenza had been carefully studied in 1918–19 They concluded that except for a lesser severity manifested especially by freedom from pneumonia the later outbreak bore a striking resemblance to the 1918 pandemic

20 HIRST George K The agglutination of red cells by allantoic fluid of chick embryos infected with influenza virus Science 94 22 1941

When the allantoic fluid from chick embryos previously infected with strains of influenza A virus was being removed it was noted that the red cells of the infected chick coming from ruptured vessels were agglutinated in this fluid Since red cells in the allantoic fluid of chick embryos inoculated with sterile materials were not agglutinated at all it seemed that this phenomenon might be the result of infection with influenza virus in the chick

This fundamental observation made possible a relatively simple method for isolating and concentrating influenza virus since the adsorbed virus can be released from the red cells and recaptured It has also made possible a simple test for antibodies because virus neutralized by immune serum no longer agglutinates chicken red cells

In other papers ("The quantitative determination of influenza virus and antibodies by means of red cell agglutination" J Exper Med 75 49 1942 "Adsorption of influenza hemagglutinins and virus by red blood cells" *ibid* 76 195) Hirst elaborated the whole subject and pointed out that by testing the inhibition of red cell agglutination one can obtain quantitative data on the titer of immune sera and also that the degree of agglutination was proportional to the concentration of virus in the test material

Hirst also made the important observation ("Adsorption of influenza virus on cells of the respiratory tract," J Exper Med 78 99 1943) that influenza virus was adsorbed by the cells of the excised ferret lung as well as by the lung of the living ferret

Cultivation of virus in chick embryo and the red cell agglutination tests have made viral and immunological studies of influenza relatively simple

21 HIRST George K Studies of antigenic differences among strains of influenza A by means of red cell agglutination J Exper Med 78 406 1943

Hirst showed that within the group of type A influenza viruses there were strains of different antigenic patterns It was found that certain epidemics were caused by multiple strains The implications for vaccination against influenza virus are obvious The subject was elaborated by T Magill and J Sugg ("The significance of antigenic differences among strains of the A group of influenza viruses" J Exper Med 80 1 1944) Sugg and Magill (Significance of antigenic differences among strains of influenza A virus in reinfection of ferrets Proc Soc Exper Biol & Med 63 1 1946) later showed that ferrets immune to clinical reinfection with the same strain of virus were susceptible to

another strain antigenically related to but different from that used for the original infection (see also Refs 15 18)

22 CHAMBERS Leslie A HENLE Werner, LAUFFER Max A and ANDERSON Thomas F Studies on the nature of the virus of influenza II The size of the infectious unit in influenza A, J Exper Med 77 265 1943

These workers thought that they had showed by ultracentrifugation of infected extra embryonic fluids of the developing chick embryo that previous estimation of the size of the virus particles (about 100 $m\mu$) was much too large Electron micrographs of the isolated virus protein indicated that the predominating unit is roughly spherical in shape and has a modal particle diameter of about 11 $m\mu$ in good agreement with the sedimentation data indicating a molecular weight of about 650 000"

The matter turned out not to be so simple however and W Friedewald and E Pickels ("Size of infective particle and hemagglutinin of influenza virus as determined by centrifugal analysis" Proc Soc Exper Biol & Med, 52 261 1943) soon claimed that the particle size was much larger The extensive studies of W Stanley ("The size of influenza virus" J Exper Med 79:267 1944) led to the conclusion that virus activity is associated with a particle diameter of about 70 $m\mu$ J W Beard and his associates working on the problem at the same time ("Ultracentrifugal, chemical and electron microscopic identification of influenza virus" Southern M J 37 313 1944), found influenza B particles to be slightly larger than influenza A particles The ultracentrifuge the electron microscope and chemical analysis were all used in this work the usual source of the virus being a concentrate obtained by adsorption on and elution from chicken red blood cells of infected amniotic fluids of chick embryos Purification and chemical composition were further studied by C Knight ("The preparation of highly purified PR 8 influenza virus from infected mouse lungs J Exper Med 83 11 1946 "The nucleic acid and carbohydrate of influenza virus" ibid 85 99 1947 "Amino acid composition of highly purified viral particles of influenza A and B" ibid 86 125 1947) R Williams and R Wyckoff ("Electron shadow micrography of virus particles" Proc Soc Exper Biol & Med 58:265 1945) devised a "shadow" technique of electron microscopy which gives vivid pictures of virus particles The present consensus as a result of much further work seems to be that influenza virus particles have a diameter of about 80 $m\mu$ (see R C Williams "The shapes and sizes of purified viruses as determined by electron microscopy" Cold Spring Harbor Symposia Quant Biol 18 185 1953) C Morgan H Rose and D Moore (Structure and development of viruses observed in the electron microscope" J Exper Med **104** 171 1956) give further data on the shape and structure of influenza virus particles

23 CROWLEY James H THIGPEN Minnie P and RICKARD E R Isolation of influenza A virus from normal human contacts during an epidemic of influenza A Proc Soc Exper Biol & Med 57:354 1944

The question of carriers of influenza virus or of subclinical infection is of course of great importance In this paper direct allantoic inoculation of throat washings from apparently healthy contacts yielded five positive results in

thirteen trials Increase in neutralizing antibodies was noted in most cases which suggested a subclinical infection but in three cases no significant increase in antibodies was found so that these individuals may have been carriers with out actual infection

Others had reported (T Francis Jr T P Magill E R Rickard and M D Beck, "Etiological and serological studies in epidemic influenza" Am J Pub Health **27**:1141 1937) increase in neutralizing bodies in the sera of individ uals exposed but without apparent infection no one had hitherto isolated virus from such cases

24 COMMISSION ON ACUTE RESPIRATORY DISEASE FORT BRAGG NORTH CAROLINA The periodicity of influenza Am J Hyg **43**:29 1946

It is impossible in this bibliography to refer extensively to the huge literature on the epidemiology of influenza This report however seems of direct impor tance to the clinician In a study of sixteen epidemics of influenza in the United States between 1920 and 1944 it turned out that influenza A occurred in a cycle of 2–3 years and influenza B in a cycle of 4–6 years The writers specu late on the significance of this periodicity

25 BURNET Frank Macfarland Some biological implications of studies on influenza viruses Bull Johns Hopkins Hosp **88** 119 1951

This is an extremely important discussion by a great authority on the subject which should be studied by everyone interested in influenza The complicated problems of transmission mechanism of infection and immunity are analyzed against the background of virus infections in general. Almost equally useful is the chapter on influenza in Burnet s book *Virus as Organism* (Cambridge Harvard University Press 1945) Burnet later summarized his views on the structure of influenza virus (Science **123** 1101 1956) with reference to mode of entry into the cells structure multiplication etc

POLIOMYELITIS 1800 TO EXPERIMENTAL TRANSMISSION (1909)

Abortive and non paralytic forms	Refs 15 16 19
Adults	Refs 2 3 6 8
Clinical description	Refs 1 2 3 6 8 10 14 15 16 19
Electrical reaction	Ref 3
Epidemiology	Refs 9 10 13 14 15 16 19
Etiology	Refs 10 13 14 15 16 19
Experimental transmission	Ref 22
General	Refs 1 19
Pathology	Refs 3 5 11 12 17
Prognosis	Ref 18
Relation to exposure	Ref 7
Relation to season	Refs 9 13 14 15 16 19
Spinal fluid	Ref 21
Terminology	Refs 1 8 19
Therapy	Refs 3 4 9

POLIOMYELITIS

A MONUMENTAL compilation sponsored by the National Foundation for Infantile Paralysis (*A Bibliography of Infantile Paralysis 1789-1949* [2d ed Philadelphia J B Lippincott Co 1951]) gives a complete list of articles and books on poliomyelitis and supplants all previous less comprehensive bibliographies However in the survey of poliomyelitis published by the Milbank Foundation (*Poliomyelitis* [Baltimore Williams & Wilkins Co 1932]) there is to be found a very useful reference list of over eight hundred titles

Valuable contemporary monographs which cover approximately the period of this bibliography are as follows

ROMER P H *Die epidemische Kinderlahmung* Berlin J Springer 1911 English translation by H RIDLEY PRENTICE *Epidemic Infantile Paralysis* London John Bale 1913

WICKMAN IVAN *Acute Poliomyelitis* Authorized translation by DR. J WILLIAM J A M MALONEY New York Journal of Nervous and Mental Disease Publishing Co 1913

MULLER EDUARD *Die spinale Kinderlahmung* Berlin Julius Springer 1910

PEABODY FRANCIS W DRAPER GEORGE and DOCHEZ A R *A Clinical Study of Acute Poliomyelitis* New York Rockefeller Institute for Medical Research 1912

1 The various early nineteenth-century accounts of poliomyelitis are brief confused and inadequate Descriptions of the disorder are included as a rule in general discussions of the paralyses of childhood Many of them deal with late stages of deformity the original cause of which is quite unrecognizable [1] However those case reports which concern a child suddenly paralyzed in one or more limbs either out of a clear sky or following some sort of an indisposition may well have had to do with poliomyelitis Modern writers credit Underwood at the turn of the nineteenth century with the first significant description of infantile paralysis However a scrutiny of his book (Michael Underwood *A Treatise on the Diseases of Children etc* [2d American ed Boston D West 1806])[2] yields little that is definite although what he describes under "Debility of the lower extremities (p 281) may perhaps have been poliomyelitis But the complaint at other times seems to arise from debility and usually attacks children previously reduced by fever It is a chronical or lingering complaint and not attended with pain fever or any manifest disease When both [legs] have been paralytic nothing has seemed to do any good but irons to the legs The position was later well summarized (1855) by Duchenne (Ref 3) who writes with reference to the older accounts I must say that if one had to depend only on the de

[1] Those who wish references to all the early case reports both definite and questionable will find them listed in the National Foundation s *Bibliography of Poliomyelitis*

[2] The earliest edition of Underwood s book in which reference is made to this disorder appeared in 1789

scriptions of these authors the diagnosis and prognosis of this disease of childhood would remain very uncertain [*dans une grande obscurité*]"

In sharp contrast to the professional accounts is the admirable description of his own case given by Sir Walter Scott in his autobiography (J G Lockhart *Memoirs of the Life of Sir Walter Scott Bart* [Edinburgh Robert Cadell 1837] 1:14) written in 1808 "One night I have been told I showed great reluctance to be caught and put to bed and after being chased about the room was apprehended and consigned to my dormitory with some difficulty It was the last time I was to show such personal agility In the morning I was discovered to be affected with the fever which often accompanies the cutting of larger teeth It held me three days On the fourth when they went to bathe me as usual they discovered that I had lost the power of my right leg"

As to terminology the first use of various designations was as follows

Debility of the lower extremities Underwood (1789) Ref 1
Essential paralysis of childhood (*paralysie essentielle de l'enfance*) Rilliet (1843) Ref 2
Acute anterior poliomyelitis (*poliomyelitis anterior acuta*) Erb (1847) Ref 8
Atrophic fatty paralysis of childhood (*paralysie atrophique graisseuse de l'enfance*) Duchenne (1855) Ref 3
Infantile paralysis Terry (1855) Kennedy (1861) Ref 2
Infantile spinal paralysis (*spinale Kinderlahmung*) Heine (1860) Ref 2

It should be remembered that exact appraisal of many of the case reports in the early literature is impossible With the etiological agent unknown with no specific diagnostic test, and without examination of the spinal fluid it is understandable that confusion should exist about a disease which is often abortive and which often shows irregular features

2 HEINE J Beobachtungen uber Lahmungszustande der unteren Extremitaten und deren Behandlung Stuttgart F H Kohler 1840

The work of Heine has been so much extolled—indeed in Germany and Scandinavia his name has been attached to the disease he described (Heine Medinsche Krankheit)—that it is difficult to make an unbiased appraisal of his observations Heine was certainly the first to collect any considerable number of cases and to describe them carefully he attempted to bring order into the subject and his monograph is clear and well written Heine believed that disease of the spinal cord was responsible for the clinical features but he had no fatal cases in his series and made no firsthand observations of the lesions "These phenomena lead us to the presumption that an affection of the spinal cord of irritative or congestive sort underlies the disease" He gives no indication, however of appreciating any specific changes in the anterior horn cells In his description of the clinical picture he emphasizes occurrence in children six to thirty six months old and in previous good health As initial symptoms there may be fever "congestive and irritative" states depression crying drowsiness and difficult teething Convulsions are frequent. In other cases convulsions nausea collapse foaming at the mouth and nose and cyanosis constitute a sudden onset Sometimes there are no recognizable symptoms and the paralysis is simply noticed As observed by others the patients rarely died and often promptly recovered even from extensive disability Some however had perma

nent weakness and Heine who was an orthopedist gives a comprehensive account of the physical therapy and rehabilitation which are necessary His monograph is illustrated with excellent drawings of deformities following paralysis and of braces applied to the legs While he emphasized paralysis of the lower extremities he also described patients with hemiplegia and paralysis of the arms

Just what all these disorders actually were it is hard to say now Peripheral neuritis and perhaps encephalitis may have been present in some cases Heine certainly deserves credit for being the first to crystallize the subject His monograph of 1840 was preceded by a more inaccessible paper ("Ueber Lahmungen die im kindlichen Alter nach Convulsionen entstehen konnen und gewohnlich von bedeutender oder peripherer Difformitat der unteren Extremitaten begleitet werden" Tageblatt d Vers deutsch Naturforsch u Aertze 1836) and was followed by other articles (Aufforderungen an praktische Aerzte" Schweiz. Monatschr f prakt Med 2 269 1857) and by his book of 1860 (*Spinale Kinderlahmung* [Stuttgart J G Cotta scher Verlag 1860]) in which he introduced the designation "infantile paralysis but otherwise added nothing essential to his monograph of 1840

Other more or less contemporary accounts some of which have been much quoted are the following

J Badham reported four cases ("Paralysis in childhood" London M Gaz 17 215 1834-35) which were probably poliomyelitis although the brief clinical descriptions are not entirely decisive From the mélange of patients reported by C West ("On some forms of paralysis incidental to infancy and childhood" London M Gaz, N S 2 829 1842-43), one may select three or four who quite definitely had infantile paralysis These very cases however in contrast to those caused by "disease of the brain" West regarded as representing a mild disorder due to teething or to measles with probably no organic lesion He appears to have been unaware of Heine s work

F Rilliet and E Barthez in their book (*Traité clinique et pratique des maladies des enfants* [Paris Germer Baillière 1843] 2 335) under the heading of "Essential Paralysis discuss sudden palsies occurring in children which may perhaps have been poliomyelitis In the one case which they report in detail the brain and spinal cord were said to show no lesion Rilliet later (De la paralysie essentielle chez les enfants" Gaz méd Paris 6, ser 3 681 1851) wrote systematically on the subject but added little to his previous remarks The account of H Kennedy ("On some of the forms of paralysis which occur in early life" Dublin J M Sc 9 85 1850) is no less confusing and deals with superficial clinical considerations Whether some of his cases were poliomyelitis or not it is impossible to say Kennedy believed that there was no anatomical lesion although he had no autopsies indeed none of his patients died Kennedy did however suggest that the same varieties of paralysis might occur in adults "I am satisfied there is much less difference between the paralysis of early and more advanced life than what might at first sight appear—I am sure I have seen in the adult all the forms of paralysis which it has been my wish to describe as occurring in the young Chaussignac s description (De la paralysie douloureuse des enfants jeunes" Arch gen de méd 1 653 1856) does not in the slightest way resemble poliomyelitis nor can anything useful be extracted

from the lectures of C E Brown-Séquard (*Lectures on the Diagnosis and Treatment of the Principal Forms of Paralysis of the Lower Extremities* [Philadelphia J B Lippincott & Co 1861]) Joseph Bierbaum a general practitioner in the town of Dorsten has an article of ninety nine pages ("Die Paralysen der Kinder" J F Kinderkr 32:18 1859) which brings out very clearly the confusion that existed in the minds of doctors about the paralyses of children "In my situation without access to libraries it is impossible to have a wide knowledge of the literature" says Bierbaum but nonetheless his article represents a good effort to straighten out the situation The main difficulties were inadequate knowledge of neuroanatomy and clinical neurology lack of fatal cases with autopsies and the widely prevailing idea that paralysis of a limb or limbs in small children could often occur as a functional disturbance without any lesion

In all these early accounts as we said one is struck by the common story of sudden complete paralysis of a limb coming out of a perfectly clear sky the lack of fatal cases and often complete rapid recovery of a totally disabled part If this disease really was poliomyelitis the clinical features and perhaps the strains of virus have clearly changed through the years—a well known phenomenon in medicine as witness syphilis typhoid fever smallpox and many others It should also be mentioned that the early writers for the most part regarded the paralysis as reflex" from some source of irritation such as teething Later hemorrhage was often blamed The actual lesion was not generally recognized until the 1870 s (Ref 5)

3 DUCHENNE DE BOULOGNE [Guillaume Benjamin Armand] Paralysie atrophique graisseuse de l enfance Paris J B Baillière et fils 1855

Aside from his achievements in neurology Duchenne was a pioneer in medical electricity his book *De l'électrisation localisée* is a classic and ran through many editions[8] By studying the electrical reactions of paralyzed children Duchenne discovered that different muscles or muscle groups were variously affected even though shortly after the paralysis the muscles did not yet appear atrophied He concluded by analogy with cases of cord injury that the lesion in infantile paralysis must also lie in the spinal cord although he did not define the histological changes Duchenne also gave an admirable clinical description of the disease he noted the frequency of fever at onset the sensory symptoms the types of paralysis and the late atrophies and deformities He designated the disease atrophic fatty paralysis of childhood but later (see the third edition of his *Electrisation* [1871]) dropped the "fatty" and spoke simply of "atrophic paralysis of childhood" At this time he thought the disease occurred only in children and could find no more plausible cause than teething Later (Ref 6) he realized that the same disease affected adults He developed electrotherapy and was able on the basis of the degree of altered electrical reaction to predict which muscle groups would recover most quickly Duchenne s observations were later elaborated in a long article ("De la paralysie atrophique graisseuse de l enfance Arch gén de méd 2 28 184 441 1864) Erb s name (Ueber

[8] English translation of the third edition *A Treatise on Localized Electrization etc by Dr G B Duchenne* translated by Herbert Tibbits M D (London Robert Hardwicke 1871)

Poliomyelitis anterior chronica nebst Bemerkungen uber die diagnostische und pathologisch physiologische Bedeutung der Entartungsreaction," Arch. f Psy chiat 8 216 1878) is also prominently associated with interpretation of electrical reactions in cases of poliomyelitis

4 TAYLOR Charles Fayette Infantile paralysis and its attendant deformities Philadelphia J B Lippincott Co, 1867

Even in the earliest accounts of poliomyelitis attention was directed toward treatment As early as Underwood (Ref 1), the need of braces for the late deformities was recognized. Heine gives a detailed discussion of this phase in his books (Ref 2) Other measures both medical and physical including electrical treatment were discussed by such writers as Duchenne and Taylor

In view of the modern Kenny treatment it is of interest to note that Taylor as long ago as 1867 fully recognized the value of heat in general and of hot packs in particular for the first stages of the disease "All those who have had experience in these cases have recommended the warm or hot local bath as of great value My experience is that the value of local heat in these cases cannot be overestimated" Taylor also gives a sophisticated account of the mechanism of production of deformities their prevention and their treatment by orthopedic methods and appliances He noticed furthermore that the incidence of infantile parlysis was increasing rapidly in this country

5 CHARCOT J A., and JOFFROY A. Cas de paralysie infantile spinale avec lésions des cornes antérieures de la substance grise de la moelle épinière Arch de physiol 3 134 1870

It is very difficult to decide who deserves credit for first describing the nature of the spinal cord lesion in infantile paralysis All the early reports dealt with autopsies of patients whose paralysis had occurred months to many years before death Charcot s case for example concerned a girl who at the age of six, following an indisposition of some sort, suddenly lost the use of arms and legs without sphincter disturbance or sensory loss There was some gradual recovery in the arms but little return of power in the legs At the time of her death twenty years after the acute phase there were of course severe atrophies and contractures The writers described in detail the gross appearance of muscles and spinal cord they showed in excellent drawings the atrophy of the anterior horns They pointed out that certain muscles had become transformed into fibrous strands others "conserved their normal bulk, but almost all the tissue was replaced by fat through which ran reddish shreds which are nothing else than muscle fibers" A section through the cord (cervical) showed that "the anterior horns are wasted and deformed No traces of nerve cells are any longer found." Charcot correlated the degree of damage in the cord with the extent of the muscular atrophy "The alterations which we have described are clearly nothing more than the vestiges of a pathological process whose activity is long since extinct" He doubted current views that hemorrhage or softening was the original lesion Why this remarkable localization in the area of the anterior horns if the neuroglia was first affected? Is it not more probable that the motor nerve cells whose function is so specialized were the primary seat of the disease?" This point of view was elaborated in another paper ("Groupe des

myopathies de cause spinale–paralyse infantile Rev phot d'hôp de Paris 4:1 1872)

V Cornil ("Paralyse infantile" Compt rend Soc de biol 5, 3d ser 187 1863) had previously reported from Charcot's clinic what appears to be a dubious case It concerned a forty nine-year-old woman whose feet were said to have been paralyzed from the age of two years She died of cancer of the breast The cord lesion was described as "an atrophy of the anteroposterior tracts [*faisceux*] of the cord with production of amyloid bodies through its extent." The case of J I Prevost ("Observation de paralysie infantile lésion des muscles et de la moelle" Compt rend Soc de biol 2, 4th ser 215 1865) is also unsatisfactory the patient died at seventy-eight years of age and the story of the childhood paralysis is obviously vague At autopsy there was a purulent meningitis However many of the anterior roots were atrophic and there was atrophy of cells of the anterior horns corresponding to the innervation of the paralyzed foot so the case may well have been an old poliomyelitis The much-quoted report of Lockhart Clarke and Hughlings Jackson ("On a case of muscular atrophy etc" M Chir Tr 32 489 1867) however obviously concerns a patient with amyotrophic lateral sclerosis and not poliomyelitis

It was not until much later (Ref 12) that the lesions of the acute attack were described although F C Turner (Tr Path Soc. London 30 202 1879) gives an excellent and comprehensive description of the pathology of a cord from a child who died only two months after onset of paralysis He noted that the main changes were in the anterior horns and pointed out perivascular cuffing by leukocytes

Roger and Damaschino (Compt rend Soc de biol 23 49 1871) carried the subject along with anatomical studies from which they concluded that the characteristic alteration is a lesion of the spinal cord of which the atrophy of nerves and muscles is the result" They localized the lesion especially in the anterior horns and pointed out that "the softening is inflammatory in nature and the disease is a myelitis"

It was not however until the twentieth century that comprehensive descriptions of the pathology of poliomyelitis in the modern sense became available (see I Wickman in M Lewandowsky *Handbuch der Neurologie* [Berlin J Springer 1911] 2 807)

6 DUCHENNE (DE BOULOGNE) De l'électrisation localisée etc pp 437 ff 3d ed Paris J B Baillière et fils 1872

Although Kennedy (Ref 2) and perhaps others thought that poliomyelitis could occur in adults it was generally regarded as affecting only small children Duchenne however reported quite typical cases in older people He concluded (p 444) "There have been no anatomical reports on cases of acute spinal paralysis of adults but reasoning by analogy one reaches this conclusion If one considers the resemblance of symptoms course and termination of this disorder in adults to the findings in children where the pathology of the cord is well known one must conclude that the same lesion will be found in adults—atrophy of the anterior horn cells of the cord

Many papers soon followed confirming this point of view Combault (Arch de physiol 5 80 1873) described two supposed cases of poliomyelitis in men

aged thirty five and forty years[4] and also an instance in a girl of seventeen who came to autopsy seven years later with a lesion practically confined to "the large motor cells of the anterior horns M Bernhardt ("Ueber eine der spinalen Kinderlahmung ahnliche Affection Erwachsener" Arch f Psychiat 4 370 1873) reported several more typical cases in adults and from this time on it was generally accepted that poliomyelitis was not confined to infants

7 EISENLOHR C Zur Lehre von der akuten spinalen Paralyse Arch f Psychiat 5 219 1875

The idea that physical strain or exposure in the early stages of poliomyelitis had a detrimental effect on the course of the disease is often set forward as a modern concept This view was however emphasized in many reports as long ago as seventy five years Eisenlohr for example tells of a man of thirty three who went home in the cool of the morning lightly clad after dancing all night (*nach einer durchtanzten Nacht*) and then developed progressive motor weakness in the lower extremities The same point is vividly brought out by T Althaus (On acute anterior myelitis in the adult" Am J M Sc 75 409 1878) He tells of a man who was out taking exercise in a very powerful sun and toward evening took a bath in the sea "The water felt very chilly but he never the less remained about three quarters of an hour in it On coming out at last he felt benumbed and in the night had acute pain in the small of the back and legs During the next day he had difficulty walking which rapidly went on to paralysis Bull (Sub acute spinal paralysis of adults" Lancet 1 563 1880) also reported a patient in whom an interesting feature of the case was the undoubted relation of the attack to exposure"

8 ERB W Ueber acute Spinallahmung (Poliomyelitis anterior acuta) bei *Erwachsenen etc Arch f Psychiat 5 758 1875*

Erb s paper is of note because here for the first time is used the term acute anterior poliomyelitis Erb also carried the subject forward by a brilliant clinical description of the disease in which he points out that mild and severe cases are not essentially different disorders as many previously had thought but rather different phases of one spectrum One hopes to read that he went further and sensed the abortive or non paralytic cases but he did not He describes several cases in adults

9 SINKLER Wharton On the palsies of children Am J M Sc 69 348, 1875

Sinkler definitely noted that infantile paralysis is a summer disease "It is in the second summer however that most of these cases of infantile paralysis occur I have carefully noted the time of year when the paralysis came on I found that two cases in March one in April one in May eight in June eleven in July nine in August forty of the fifty seven cases were affected in the summer months "This fact has not to my knowledge been remarked before However soon after W H Barlow (On regressive paralysis [infantile paralysis spinal paralysis of adults] " Liverpool and Manchester M & S Rep

[4] One of these cases previously described by Cuming (Dublin J M Sc 47 471 1869) seems to us very doubtful and the pathological report is quite inadequate to allow any conclusions

611 1878) remarked "Of the influence of season we have strong evidence of 53 cases 27 occurred in the months of July and August" Barlow s ideas of why this was so seem fanciful now but his facts are important Under treatment he emphasized moist heat— hot flannels and cloths dipped in the water well wrung out and applied to the paralysed parts" (see Ref 4)

Sinkler later ("Etiology of epidemic poliomyelitis" Arch Diagnosis 1 28 1908) gives a useful list of all epidemics described to date

10 STRUMPELL Adolph Ueber die Ursachen der Erkrankungen des Nervensystems Deutsches Arch f klin Med 35 1 1884

Even after many diseases such as tuberculosis were known to be caused by a living infectious agent doctors still seemed reluctant to believe that central nervous system disorders might fall into a similar category Strumpell the great German clinician in a general lecture on the causes of disease of the nervous system seems to have been the first to insist that poliomyelitis as well as certain cases of "acute multiple neuritis" and acute encephalitis of children were infectious and probably were caused by similar agents Thus he widened the concept of poliomyelitis the lesions of which were previously regarded as confined to the spinal cord "All these illnesses begin rather abruptly with fever often of considerable degree The patients are dull have headache gastro intestinal disturbances etc" "According to present views these are all symp toms which point to an infection of the body with an organized disease pro ducer" The weight of Strumpell s authority was important in promoting these views but it was of course the appearance of poliomyelitis in epidemic form within the next decades which made the significance of infection obvious

In a paper appearing in the following year Strumpell ("Ueber die acute Encephalitis der Kinder Jahrb f Kinderh 22 173 1885) pursued further the relationship between classical poliomyelitis and acute encephalitis of chil dren Both disorders usually attack healthy young children There is an acute initial stage which is hardly to be distinguished in the two conditions Then there remains a paralysis in one case of cerebral origin in the other of spinal origin Strumpell of course had no specific tests available and his cerebral cases may have been various kinds of encephalitis but he clearly widened the concept of poliomyelitis beyond the classical limits of a spinal disease "I myself incline to the assumption that both disorders are essentially related or indeed identical in the sense that in both the same (perhaps infectious) agent attacks in the one case the gray matter of the cord, in the other the gray matter of the cortex" This position was confirmed by the studies of Medin and of Wickman (Refs 14 19)

The contemporary views on poliomyelitis are admirably summarized in Strumpell s textbook (*Lehrbuch der speciellen Pathologie und Therapie etc* [4th ed Leipzig F C W Vogel 1877] 2 255) The role of infection as well as communicability is especially emphasized

11 DRUMMOND David On the nature of the spinal cord lesion in polio myelitis anterior acuta or infantile paralysis Brain 8 14 1885–86

Most of the early reports on the pathology of poliomyelitis dealt with subjects who died long after the acute disease Drummond reports a patient who died

only 7 hours after the onset of symptoms presumably of respiratory paralysis Proof of the etiology is of course not absolutely complete However there were extensive changes especially in the anterior horns where the "large cells formed prominent objects although they were apparently swollen granular and rather ill-defined The cells that presented the most obvious changes were more or less surrounded with dilated and blocked capillaries and minute hemorrhages This is the first report we can find on the pathology of polio myelitis in the very early stage

12 RISSLER J Zur Kenntnis der Veranderungen des Nervensystems bei Poliomyelitis anterior acuta Nord med ark 20 1 1888

While Drummond (Ref 11) preceded Rissler in describing the pathological changes of poliomyelitis early in the acute stage Rissler s careful study is the first to deal with the subject in comprehensive fashion He reports autopsies on patients who died respectively on the sixth and eighth days of the disease He emphasizes the degeneration of anterior horn cells but points out variations in the severity of the lesion in different cells in the same region He also demonstrated changes in the motor cranial nerves as well as lesions elsewhere in the nervous system such as the posterior horns and Clarke s columns Rissler observed lesions outside the central nervous system such as enlargement of spleen and lymph nodes

A review of the most important contemporary articles on the pathology of poliomyelitis is given by G von Kahlden ("Neuere Arbeiten über Poliomyelitis anterior acuta " Centralbl f allg Path 5 729 1894)

13 CORDIER S Relation d une épidémie de paralysie atrophique de l enfance Lyon méd 57 5 1888

Although credit for first suggesting the occurrence of poliomyelitis in epidemic form is usually given to George Colmer (Am J M Sc 31 248 1843) one finds in his article only a brief paragraph in which he says "The parents told me that eight or ten other cases of either hemiplegia or paraplegia had occurred during the preceding three or four months within a few miles of their residence " Cordier however on the basis of thirteen cases of infantile paralysis occurring over a 2-month period (June July) in a town of fourteen hundred people says "In showing that the atrophic paralysis of childhood can occur in epidemic fashion these cases will show also I hope that this paralysis is a specific infectious disease one might say microbial " He also concludes "And for my part I would not hesitate to isolate [*éloigner*] young infants if I saw infantile paralysis appear in their neighborhood "

While there are in the early literature hints of other outbreaks it remained for Medin (Ref 14) to describe a frank epidemic

14 MEDIN O Ueber eine Epidemie von spinaler Kinderlahmung Verhandl d X Internat med Kongr (August 1890) Berlin, 2 37 1891 see also Hygeia 52 657 1890

It seems improbable that the presence of so striking a disease as poliomyelitis could be overlooked one must conclude therefore that poliomyelitis actually did not occur in epidemic form until the last decades of the nineteenth century The outbreak described by Medin is the first of any large proportions (but see

Cordier Ref 13) and full advantage was taken by him in studying it. Ordinarily Medin saw in Stockholm only "a few" cases each year but in 1887 he observed twenty nine instances of poliomyelitis between August 9 and September 23 He was convinced that the disease was infectious but doubted its contagiousness as emphasized by Cordier Children only were affected The occurrence at the same time of various clinical types was noted and seemed to speak for a common etiology these observations supported the views previously expressed by Strumpell (Ref 10) and were of the greatest importance in widening the older concepts of the disease Aside from classical acute polio myelitis there were cases with motor cranial nerve palsies as evidenced by failure of respiratory muscles hoarseness difficulty in swallowing double vision etc and cases with polyneuritis and with polioencephalitis Emphasis was placed on the severity of the acute attack which was fatal in a number of children Medin emphasized fever somnolence pain, and muscle tenderness

This study was of course of great significance and should be read in detail by every student the German clinicians were sufficiently impressed later to rename the disease "die Heine-Medinsche Krankheit" (Ref 19) But most important of all seems to be the fact that there must have been an actual change at about this time in the natural history of poliomyelitis Previously benign (as to survival) and sporadic, epidemics from this time on have been frequent, with many acutely fatal cases

Medin s views were elaborated by him on the basis of further experiences in 1896 (Nord. med. ark., 6:1) This article is more accessible in a French translation ("L'État de la paralysie infantile" Arch. de méd d. enf 1 257 321 1898) The clear description of the early phenomena such as somnolence intestinal symptoms hyperesthesia etc is especially important Medin widened the concept of poliomyelitis from that of a localized disease of the spinal cord to that of a generalized infection

15 CAVERLY C S History of an epidemic of acute nervous disease of unusual type M Rec 46 673 1894

"During the month of June 1894 there appeared in a portion of the valley of the Otter Creek in the State of Vermont, an epidemic of nervous disease in which the distinctive and most common symptom was paralysis" The outbreak is described in vivid style by C S Caverly of the Vermont Board of Health, and is a model of precise reporting The outbreak was confined to a narrow region around the city of Rutland There were over 125 cases The clinical picture was typical of epidemic poliomyelitis as we now know it but Caverly noted the many deviations from the standard contemporary accounts "It is at once noticed that individual cases can be readily recognized as presenting a typical picture of poliomyelitis anterior but that the variations from the text book type of this disease are many and marked Opisthotonos eye symptoms and hyperesthesia are out of place in the phenomena of this disease so that the epidemic, as a whole presents notable departures from the regular features of the disease" In some of the patients there was little or no paralysis Dr A Jacobi from a written description said "All your cases belong to the same class cerebrospinal meningitis" but Allen Starr and Charles L. Dana believed them to be poliomyelitis Caverly was familiar with "Medin s [*sic*]

account" and he concluded Under the newer pathology given of poliomyelitis, symptoms referable to the meninges and cerebral ganglia can be reasonably explained" Caverly went wrong on one important point he considered the disease to be non contagious

The importance of Caverly's report rests first of all on his admirable description of the first epidemic of poliomyelitis in this country Even more significant, however is the evidence that poliomyelitis in outbreaks of this sort differs in its natural history from the classical sporadic disease The possibility is strong that the epidemics so frequent from this time on may have been due to new or different strains of virus Caverly later redescribed the Vermont epidemic in the Journal of the American Medical Association ("Notes on an epidemic of acute anterior poliomyelitis," 26 1 1896) but nothing new is added An interesting point is that during the epidemic various domestic animals were *said to have died paralyzed*

Later Joseph Collins ("Acute anterior poliomyelitis or acute spinal paralysis of children remarks on the epidemic now prevailing in New York" M Rec 72 725 1907) gave an account of the first really large American epidemic that in New York City in the summer of 1907 There were said to be over twenty five hundred cases mostly in young children The writer had no ideas on etiology but advised lumbar puncture on the slightest suspicion A valuable report on this epidemic which summarizes contemporary knowledge of the whole subject was that of a committee of the New York Neurological Society (J Nerv & Ment Dis 36 619 1909)

16 PASTEUR W An epidemic of infantile paralysis occurring in children of the same family Tr Clin Soc London 13 143 1897

Caverly (Ref 15) thought poliomyelitis was non contagious because it was unusual for more than one child in a household to be affected Pasteur however describes an interesting family "epidemic" in which "early in June the whole seven [children] were attacked in rapid succession within the space of ten days" But the heretofore unique feature of the outbreak was that all forms of the disease occurred in this small group—some with typical paralysis *some with cranial nerve lesions some with fever but no paralysis* The etiological unity of various clinical forms as well as contagiousness seemed then to be proved beyond question

During succeeding decades most students of the disease came to believe that it was infectious but many doubted its communicability from person to person *L E Holt and F H Bartlett* (*The epidemiology of acute poliomyelitis a study of thirty five epidemics*" Am J M Sc 135 647 1908) on the basis of a careful analysis of the reported epidemics stated "We cannot resist the conclusion that the disease is communicable although only to a slight degree Even now fifty years later the finer details of transmission have not yet been worked out

17 WICKMAN Ivar Studien uber Poliomyelitis acuta Arb a d path Inst d Univ Helsingfors 1 109 1905

This the first to be published of Wickman's important studies on poliomyelitis is a rather *ponderous treatise of some one hundred pages dealing chiefly with* the pathological changes Wickman's main point was that the lesions were not

limited to the anterior horns but were much more widespread Item 1 of his conclusions for example says "An infiltrative myelitis lies at the basis of poliomyelitis This occurs in scattered foci and is therefore to be thought of as a disseminated myelitis The disseminated character is especially evident in the medulla oblongata and in the brain where in my cases changes if sought for were always present"

Many of Wickman s patients died early in the disease and some ran a course like "Landry s" paralysis Wickman did the subject good service in widening the concept of poliomyelitis but without virus stud es one cannot now be sure of the identity of all his cases

Wickman speculated on the route of infection whether hematogenous lymphogenous or along the nerves but again his material and methods prevented him from progressing beyond the philosophical stage His experiments with the injection of banal bacteria into the arteries of the cord have little significance in the light of modern knowledge

18 WICKMAN Ivar Ueber die Prognose der akuten Poliomyelitis und ätiologisch verwandter Erkrankungen Ztschr f klin Med 63 362 1907

Wickman points out that before the Swedish epidemic described by Medin poliomyelitis was regarded as a disease rarely fatal even if disability persisted He analyzed the Swedish material and found that, among 1 025 cases 145 patients died before the fifteenth day of the disease a death rate of 12.2 per cent. He also points out that the mortality was higher in older children and in adults (28–33 per cent) than in younger children These percentage figures applied only to overt paralytic cases

19 WICKMAN Ivar Beitrage zur Kenntnis der Heine Medinschen Krankheit Berlin S Karger 1907

"With the name of Heine-Medin disease I designate a whole group of illnesses which are united because of a common etiology indeed they are caused by a specific virus of infectious nature In the center of the picture stands infantile paralysis But many cases deviate from this they may present symptoms and signs pointing to parts of the nervous system other than the spinal cord such as the brain bulb or meninges or they may run the course of a generalized infection without demonstrable localizing signs" So begins Wickman s classical monograph which is just as exciting as his previous report (Ref 17) is dull It was the occurrence in epidemics which made possible the clear recognition of these variations in the clinical picture of poliomyelitis Wickman distinguished (1) the poliomyelitic form (classical infantile paralysis) (2) the form showing an ascending paralysis (Landry s paralysis) (3) the bulbar or pontine form (4) the encephalitic form (5) the ataxic form (6) the polyneuritic form (7) the meningitic form and (8) the abortive forms Thus he brought system and order to what had already been roughly recognized A special contribution was the description of the abortive forms although many of Wickman s cases would today be described as non paralytic rather than abortive since fever and general symptoms were marked. The symptoms were aches and pains headache hyperesthesia diarrhea fever etc It was the occurrence of paralytic forms at the same time in the brothers or sisters which made

Wickman sure that the non paralytic forms were caused by the same agent These findings also spoke for contagion but his chief evidence of communicability was the tracing of successive cases in rural communities where it was shown that contact in school for example was paramount in the spread of the disease These detailed studies are of the greatest interest. Wickman was the first then clearly to describe epidemic spread and thereafter no one seriously questioned the contagiousness of poliomyelitis Wickman stated that "contact does not have to be direct On the contrary it often seems to be true that contact is mediated by a healthy intermediary" Thus he clearly raised the question of carriers which he said are well known to be of importance in the epidemiology of various infectious diseases As to etiology ordinary bacteriological studies were negative in Wickman's hands but he was convinced that there was a specific infectious agent, which was soon to be established by others (Ref 26) Wickman tells in detail (pp 5-9) why he feels that the name "Heine Medin disease" is appropriate

This monograph should be carefully read by any serious student of the disease It is not to be confused with a later brief summary (in Lewandowsky *Handbuch der Neurologie* [Berlin J Springer 1911] 2 807) from which the English translation is taken ("Nervous and Mental Disease Monograph Series" No 16 [New York 1913])

20 BUZZARD E Farquhar On certain infective or toxic conditions of the nervous system Brain **30**:1 1907

Buzzard describes in great detail the pathology of a man of twenty six years who died from respiratory failure within 24 hours of the onset of paralysis

21 GAY Frederick P and LUCAS William P Anterior poliomyelitis methods of diagnosis from spinal fluid and blood in monkeys and in human beings Arch Int Med **6** 330 1910

Primitive efforts to examine the spinal fluid in cases of poliomyelitis usually consisted in staining centrifuged material and making bacteriological cultures Various organisms—obviously contaminants or secondary invaders in the light of present knowledge—were seen or were grown and cells of various sorts were described in the stained sediment Thus F Schultze ("Zur Aetiologie der acuten Poliomyelitis Munchen med. Wchnschr **45** 1197 1898) saw what he believed to be meningococci F Engel (Bakteriologisches Ergebniss einer Lumbalpunction bei Poliomyelitis acuta" Prag med Wchnschr **25** 135 1900) drew 30 cc of clear spinal fluid from a boy on the sixth day of acute poliomyelitis No cells were seen but various bacteria grew In F X Dercum's case (Note on a case of acute poliomyelitis in which the cerebro spinal fluid obtained by a Quincke puncture contained a diplococcus resembling the diplococcus of Sternberg J Nerv & Ment Dis **27** 116 1900) "a few leucocytes" were seen Triboulet and Lippmann ("Poliomyélite antérieure aigue ponction lombaire mononucleose *Bull et mém Soc méd d hôp de Paris* **19** 23 1902) found that fluid drawn on the twenty fourth day showed many "mononuclear lymphocytes" but no "polynuclears" and L Guinon and Paris ("Paralysie infantile avec réaction méningée Bull et mém Soc méd d hôp de Paris **20** 673 1903) on the thirteenth day also found numerous "lymphocytes but no

bacteria C Achard and H Grenet ("Paralysie infantile et lymphocytose arachnoidienne" Rev neurol 11:345 1903) report similar findings M Wollstein ("A biological study of the cerebrospinal fluid in anterior poliomyelitis J Exper Med 10:476 1908) examined fluid from eleven cases during the first 2 weeks In centrifuged smears "one to three mononuclear leucocytes were found but large numbers were never present These variable and inadequate examinations were superseded by the careful studies of Gay and Lucas who appear to be the first to have made accurate counts of the cells of the spinal fluid in poliomyelitis both in the monkey and in man Counts were made in 14 cases of poliomyelitis from the second to the seventeenth day The number of cells varied from 50 to 580 per cubic millimeter almost all were "mononuclears" or "lymphocytes" The leucocyte counts of the blood varied from 7 800 to 17 400 usually with increase in lymphocytes

22 LANDSTEINER Karl and POPPER Erwin "Uebertragung der Poliomyelitis acuta auf Affen Ztschr f Immunitatsforsch u Exper Therap 2 377 1909

This article is a landmark in the subject since it really marks the beginning of the modern experimental study of poliomyelitis The authors point out that, on the basis of epidemic occurrence everyone agreed that the disease was infectious in origin The alleged claims that animals—horses chickens rabbits—developed paralyses during outbreaks of human poliomyelitis are reviewed and discredited The claims for a bacterial cause are thoroughly discussed The writers point out that whereas many bacteria such as meningococci pneumococci staphylococci streptococci and others have been incriminated no consistent findings have been obtained by various workers and indeed a number of reliable observers have been unable to isolate any bacteria from spinal fluid or nervous tissues of poliomyelitis cases [5]

Landsteiner and Popper s own experiments were not made primarily with the idea of searching for a filtrable virus but simply to see whether the disease could be transmitted to animals They worked with emulsions of the spinal cord of a boy dead of poliomyelitis and made intraperitoneal injections into rabbits guinea pigs mice and monkeys Cultures of the material yielded no growth by the usual bacteriological methods The rabbits guinea pigs and mice remained well but the monkeys came down with typical poliomyelitis One died 8 days after inoculation and the spinal cord showed outspoken lesions The second animal became paralyzed in the lower legs Injection of material from this animal into other monkeys was ineffective and it remained for others to transmit the disease in series The final conclusion of the authors was "The presumption is therefore strong that a so-called invisible virus or one belonging to the class of Protozoa is the cause of the disease

This work was first announced on December 18 1908 at a meeting of the Gesellschaft der Aerzte in Vienna (see Mikroskopische Praparate von einen menschlichen und zwei Affenruckenmarken Wien klin Wchnschr 21 1830 1908) A tiny note to the same effect by Landsteiner ("Poliomyélite antérieure

[5] It is of interest that as late as 1952 an article appeared in which it was claimed that streptococci were the cause of poliomyelitis (E C Rosenow California Med 76:396 195_)

ugue chez le singe" Semaine méd, 28 620 1908) also appeared in the same year

From the time of Landsteiner's work on transmission almost every phase of poliomyelitis has been under controversy Route of entry of the virus excretion presence *in various regions such as the bowel nasopharynx* and lymph glands *the question of viremia—all have been subjects of lively dispute Volumes have* been written on modes of transmission and etiology and the exact merits of various vaccines have been questioned *The subject is evidently not ripe as yet for a review such as ours perhaps in fifty years these problems* will have resolved themselves At present even experts in the subject disagree among *themselves to such a point that it would be foolish to rush in A comprehensive* list of recent references on poliomyelitis may however, be found in the bibliography of the National Foundation (*op cit*)

I am greatly indebted to my colleague Dr Harold K Faber for invaluable advice and assistance in preparing this section of the bibliography

Section 23

THE COMMON COLD

Antibiotics in colds	Ref 20
Antihistamines in colds	Ref 19
Bacteriology of colds	Ref 7
Clinical	Refs 1 8 13
Cold trauma	Refs 6 13
Cultivation of virus	Refs 11 21 22
Epidemiology	Refs 8 12
Etiology	Refs 2 5
General	Refs 1 7 13 17 18
Pathology of colds	Ref 9
Virus in colds	Refs 3 4 10 14 15 16

Section 23

THE COMMON COLD

THE pertinent literature on the common cold is not very extensive First of all a cold is for the most part a mild indisposition which most doctors have not thought worthy of very careful study Second until recent years—indeed, even now—the true infectious cold has been confused with secondary complications such as sinusitis which are not really colds at all as well as with the results of exposure to cold—cold trauma Later on in the bacteriological era the cold was blamed on almost any bacteria which could be grown from the upper air passages it was not until the normal flora transients and focal carriage of bacteria were worked out in the early 1920's that it became clear that most of the previous etiological claims had dealt with members of the normal flora and the way was clearly opened for virus studies There seems no doubt now that the common cold can be produced by instillation of filtrate of secretions from people with colds Beyond this the problem is still unsolved the agents isolated by various workers have had different characteristics and while growth has been claimed by some in chick embryos or in culture media no constant visible changes are reported Aside from monkeys no animal has definitely been infected But with the recent immense developments in the technique of virus culture the problem may soon be solved For the literature to 1932 one should consult the monumental review by David and Robert Thomson *The Common Cold* ("Annals of the Pickett Thomson Research Laboratory" Vol 8 [London Baillière Tyndale & Cox 1932])

1 HAYES T A serious address on the dangerous consequences of neglecting common coughs and colds with successful directions how to prevent and cure consumptions 4th ed Dublin L White 1786

In this admirable little treatise contemporary views are well summarized. "A cold arises from the effect of cold or moist air applied to the surface of the body and lungs from going too thinly clad or exposing the body to cold air after having been heated by exercise or when the pores are opened from drinking warm liquors" Hayes gives a good description of the clinical features of the common cold in which the primary disease is well differentiated from its sequelae One cannot be sure of course that all of Hayes's cases were infectious colds and not instances of cold trauma (Ref 18)

2 WALSH James J The etiology of colds M News New York 82 481 1903

The views of Hayes (Ref 1) were pretty much accepted until the bacteriological era Walsh points out that mere exposure to cold as a rule does not suffice to bring on "a cold." He feels that "so-called cold in the head or rhinitis is almost surely due to bacterial infection" Walsh's idea was that the "cold" is caused by any bacteria which happen to be present in the upper air passages provided that resistance is lowered usually by exposure to cold draughts coming out of an overheated room etc N James ("Colds and the prevention of colds" M News New York 86 1123 1905) held much the same view "The

mucous membrane of the nose and pharynx has upon its surface a large number of many varieties of bacteria When congestion develops the amount of mucus is increased and these organisms are supplied with more material to thrive upon" In general the standard view until the 1920s despite the work of Kruse (Ref 3) and of Foster (Ref 4) was that a cold trauma lowered resistance to a non specific infection with any bacteria at hand

3 KRUSE W Die Erreger von Husten und Schnupfen Munchen med Wchnschr 61 1547 1914

The modern study of the common cold really begins with Kruse s work He was not satisfied with the causal role of ordinary bacteria and deliberately looked for a filter passing agent Diluted filtered secretions from a patient with a cold were instilled into the nares of thirty six volunteers of whom fifteen or 42 per cent came down with a cold after an incubation period of 1–4 days Cultures of the filtered material were sterile Kruse suggested the name aphanozoa" ("invisible) for the whole group of filterable organisms and *A coryzae* for those responsible for colds

4 FOSTER George B Jr The etiology of common colds the probable role of a filterable virus as the causative factor a preliminary note J.A M.A 66 1180 1916

Foster repeated and confirmed Kruse s (Ref 3) observations in nine out of ten volunteers His filtrates were also sterile by ordinary culture methods Foster using a method modified from Noguchi thought that he was able to grow from the filtrate a tiny globoid organism Although this finding has not been con firmed Fosters paper remains a model of precise work Foster later (The etiology of common colds" J Infect Dis 21 451 1917) reported his studies in detail He thought that he had produced colds in volunteers with intranasal instillation of the second generation of the small anaerobic organism which he had grown in culture Peter K Olitsky and James E McCartney (Studies on the nasopharyngeal secretions from patients with common colds" J Exper Med 38 427 1923) later confirmed the work of Kruse and of Foster on trans mission but were unable to grow from filtered secretions either the globoid bodies described by Foster or any constant pathogenetic agent On the other hand in quite extensive experiments in which filtered nasal secretions were sprayed onto the nasal mucosa of one hundred volunteers no convincing evi dence of having produced any disease was obtained by Robert C Robinson and Robert L Groves (Experimental human inoculations with filtered nasal secre tions from acute coryza" J Infect Dis 34 400 1924) These writers also give a review of the literature

Thus even early there were conflicting experimental results the clinical dif ficulty of being sure that a true cold had been produced and not some non specific irritation may have been an important factor

5 VOORHEES Irving Wilson Colds—their cause and cure Am Med 12 125 1917

By this time the writer spoke of the cold germ or *Micrococcus catarrhalis* al though he realized that "a number of micro-organisms are usually found to gether and their team work is so perfect that they often resist all ordinary

simple remedies Voorhees laid less stress on cold as a predisposing factor and more on contagion than on "auto-infection" "Perpetual warfare ought to be waged against those who wilfully cough and sneeze into the open without protecting the face with a handkerchief Treatment was as effective in 1917 as in 1957 "a purgative hot mustard footbaths quinine and whiskey aspirin Turkish bath etc although Voorhees advised consulting a nose and throat specialist "who can see just where the trouble is and treat it accordingly" Cleaveland Floyd ("The common cold in relation to certain micro-organisms and its treatment with bacterial vaccines" Boston M & S J 182 389 1920) went further in considering the cold as a purely bacterial infection predominantly with streptococci and pneumococci, and he advocated energetic vaccine therapy He fell into error by not understanding that he was dealing with the normal bacterial flora of the throat as did many other writers at the time (see A L Bloomfield "The significance of the bacteria found in the throats of healthy people Bull Johns Hopkins Hosp 32 33 1921)

6 SCHADE H Beitrage zur Umgrenzung und Klarung einer Lehre von der Erkaltung Ztschr f d ges exper Med 7 275 1919

In this comprehensive article on the influence of cold on the body Schade points out certain definite effects on the mucous membranes of the upper air passages These are reflex vasomotor changes which may lead to anemia or hyperemia and also to direct irritative phenomena Schade describes very clearly a so called "cold catarrh" which must be differentiated from a true cold (Ref 7) and which has led to much confusion in the literature Its features are onset during or directly after the cold trauma with rawness and secretion The mucous membranes may appear reddened. There is no fever and the disturbance which is purely local lasts only 1 or 2 days Schade thought that this cold catarrh might allow bacterial invasion with secondary effects Schade in later papers (Untersuchungen in die Erkaltungsfrage" Munchen med Wchnschr 66:1021 1919 *ibid* 67 449 1920) pursued the matter further in seventeen thousand men at the front in World War I J A Miller and W C Noble (The effects of exposure to cold upon experimental infection of the respiratory tract" J Exper Med 24 223 1916) review the experimental work on the relation of cold to infection and report experiments to the effect that respiratory infection of rabbits with *Bacillus bovisepticus* is favored by chilling S Mudd and S B Grant (Reaction to chilling of body surface" J M Research 40 53 1919) and S Mudd M D Goldman and S B Grant ("Reactions of the nasal cavity and postnasal space to chilling of the body surface" J Exper Med 34 11 1921) also showed that chilling of the body surface causes vasoconstriction and ischemia in the mucous membranes of the palate pharynx and tonsils Finally in a comprehensive paper Stuart Mudd Samuel B Grant and Alfred Goldman ("The etiology of acute inflammations of the nose pharynx and tonsils Ann Otol Rhin & Laryng 30 1 1921) review in detail the ideas to date on the etiology of colds Kerr and his associates later pursued the subject of the effect of cold and heat on nasal mucosa (H J Ralston and W J Kerr "Vascular responses of the nasal mucosa to thermal stimuli with some observations on skin temperature Am J Physiol 144 305 1945)

7 BLOOMFIELD Arthur Variations in the bacterial flora of the upper air passages during the course of common colds Bull Johns Hopkins Hosp 32 121 1921

Bloomfield clearly defined the clinical features of the true common cold He emphasized that the uncomplicated cold was a mild disease featured by a constitutional reaction and by local hyperemic phenomena in the upper air passages The primary disease was to be sharply differentiated from bacterial complications such as bronchitis sinusitis otitis and also from cold trauma He reviewed the earlier literature and pointed out how little had really been written on the disease probably because of its lack of clear definition and how fanciful many of the ideas of writers on the subject were

His main contribution however was the making of repeated quantitative throat cultures in ten people with colds during the attack and over weeks or months thereafter "The cultural studies fail to show in uncomplicated cases any variation in the flora which would enable one to select any organism as the cause of colds On the other hand where complications occurred pathogenic organisms were definitely associated with them therefore the primary cause of colds is probably an organism as yet unknown But the primary cold, whatever its cause alters the mucous membranes in such a way as to allow secondary bacterial invasion and consequent frequent development of local complications" G S Shibley F M Hanger and A R Dochez ("Observations of the normal bacterial flora of nose and throat with variations occurring during colds" J Exper Med 43 415 1926) came to similar conclusions and Y Kneeland ("The relationship of bacteria to the common cold" Bull New York Acad Med 25 534 1949) later reviewed the whole subject

8 SMILEY D F A study of the weekly incidence of colds in normal and in cold susceptible groups throughout a winter Am J Hyg 9 477 1929

The writer in attempting to explain seasonal variations in the incidence of colds found that the ordinary winter or spring epidemic of colds among college students is almost entirely limited to a specially "cold susceptible" group of students Daniel F Milam and Wilson G Smillie ("A bacteriological study of colds on an isolated tropical island [St John, United States Virgin Islands West Indies]" J Exper Med 53 733 1931) concluded that there was "strong evidence that environmental factors particularly reduction in atmospheric temperature have some influence upon the incidence of colds although they believed that the cold was initiated by an infectious agent

9 HILDING Anderson The common cold Arch Otolaryng 12 131 1930

Since people do not die of colds there are few observations on the lesions Hilding however did biopsies of nasal mucosa in twenty five cases from the second hour of symptoms until the fourteenth day He describes and pictures beautifully lesions typical of a virus similar to those found in the turbinate bones of ferrets with experimental influenza as shown by T Francis Jr and C H Stuart Harris "Studies on the nasal histology of epidemic influenza virus in the ferret" J Exper Med 68 789 1938 These lesions consisted of a necrosis of the superficial epithelium with submucous round cell infiltration The epithelium was "gradually regenerated and repaired by the growth and multiplication of the stellate cells normally found deep in the epithelium" This

gradual repair no doubt accounts for the raw feeling which often persists so long after the active stages of a cold

10 DOCHEZ A R SHIBLEY Gerald S and MILLS Katherine C Studies in the common cold IV Experimental transmission of the common cold to anthropoid apes and human beings by means of a filtrable agent J Exper Med 52:701 1930

Dochez and his associates deserve full credit for reawakening interest in the search for a virus in the common cold They worked first with monkeys in which they thought that they had reproduced colds by instillation into the nasal passages of filtered nasal washings from people with fresh colds By a similar procedure colds were produced in human volunteers in four of nine cases They noted an abundance of pneumococci in the noses and throats of monkeys in the course of colds and thought that perhaps these grew on a "substrate of primary injury due to the filtrable agent" P H Long and J A Doull ("Etiology of acute upper respiratory infection [common cold]" Proc Soc Exper Biol & Med 28 53 1930) soon confirmed Dochez s work. They not only produced colds in volunteers with nasopharyngeal washings from people with colds but accomplished serial transfers through two and four individuals Their protocols are given in detail in a longer paper (P H Long, J A. Doull J M Bourn, and E McComb J Exper Med 53:447 1931)

11 DOCHEZ, A R MILLS Katherine C and KNEELAND Yale Jr Study of the virus of the common cold and its cultivation in tissue medium Proc Soc Exper Biol & Med 28 513 1931

The writers found that the virus survived for 13 days in the icebox They decided therefore to attempt to cultivate it The medium which is described in detail contained a chick embryo hash After twelve to fifteen subcultures at *intervals of 3–9 days the material still produced colds in volunteers* The writers therefore concluded that they had successfully grown an invisible agent These studies were elaborated and reported in greater detail by Dochez, Mills and Kneeland ("Studies of the common cold VI Cultivation of the virus in tissue medium" J Exper Med 63 559 1936) A little later the same workers ("Cultivation of the virus of the common cold in the chorio-allantoic membrane of the chick embryo" Proc Soc Exper Biol & Med 35 213 1936) reported implantation of *virus-containing material from a human cold on the* chorio-allantoic membrane of the chick embryo and passage through a series of three eggs Material from the third series produced a typical cold when tested on volunteers Meanwhile H M Powell and G H A Clowes ("Cultivation of the virus of the common cold and its inoculation in human subjects" Proc Soc Exper Biol & Med 29 332 1931) *found that nasal washings from patients with colds* could be grown for several generations in tissue culture and that the material then infected man in 69 per cent of trials A little later Morris Pollard and Coleman D Caplovitz ("Experimental studies with the agent of the common cold," Science 106 243 1947) reported transmission of cold virus in the chorio allantoic cavity of the chick embryo and thence to man with the production of colds and Norman H Topping and Leon T Atlas ("The common cold a note regarding isolation of an agent" Science 106 636 1947) told of producing colds in volunteers with seventh passage allantoic fluid Curiously enough C H

Andrewes ("The natural history of the common cold" Lancet 1:71 1949) a great expert in virology working with the British Common Cold Research Team although he was successful in producing "experimental colds" in 60 per cent of volunteers with bacteria free filtrates of nasal secretions from subjects with colds was entirely unable to cultivate an agent by inoculation of embryonated hens eggs by any route Andrewes very important paper takes up many other problems of the common cold Meanwhile Dochez Mills and Kneeland ("Filterable viruses in infection of the upper respiratory tract" J A M A 110:177, 1938) reviewed the whole subject of "cold virus They pointed out that unlike influenza virus it could not be established in ferrets but could in mice and that it was generally inactivated at 56° C but well preserved in the icebox anaerobically A perplexing aspect of the whole problem of cold viruses is that the various authors mentioned above all assigned quite different characteristics to their strains (Topping, Dochez, Andrewes and L. F Atlas and G A Hotter "The common cold titration of MR 1 virus in embryonated eggs" Science 108:743 1948) This suggests a multiplicity of agents The subject is further complicated by the fact that no visible changes were seen in either culture media or chick embryos even when growth appeared to have been achieved

12 PAUL J H and FREESE H L. An epidemiological and bacteriological study of the "common cold" in an isolated Arctic community (Spitzbergen) Am J Hyg 17 517 1933

There was only a very occasional cold among the inhabitants of Spitzbergen during the winter but the arrival of the first ship on May 23 was followed by a sharp outbreak of nearly two hundred cases in the two following weeks This observation which has been confirmed by similar ones with other viral infections such as measles (P Panum Ueber das Verhalten einiger epidemischen Krankheiten auf Faro Island und in Danemark," Verhandl d phys med Gesellsch in Wurzburg 3:16 1852) leaves no doubt that the common cold is caused by a living agent It seems clear that whatever transient protection has been conferred by last summer s colds if any wears off during the winter so that a highly susceptible population is available which readily becomes infected by the new arrivals It is of interest that among the new arrivals there may be no one with clinical infection which suggests that carriers may introduce the virus

There was no change in the bacterial flora of the upper air passages as previous workers (Ref 7) had also found The literature on these epidemiological observations is critically reviewed by Andrewes (Ref 14)

13 KERR William J The common cold J A M A 107 323 1936

Kerr questions the doctrine that colds are caused by a living agent This idea was based on observations in which people who were subject to colds were placed in intimate and prolonged contact with people in the early *active stages* of a cold Kerr also instilled fresh nasal secretions from people with colds into the conjunctivae of the volunteers In no case was a cold produced These observations are in line with common clinical experience on the acquisition of colds and although perhaps Kerr goes too far in questioning the need of a living agent there may be necessary in addition a resistance lowering factor (the jolt of Andrewes) which was absent in his experiments Details of

Kerr's observations may be found in a paper by W J Kerr and J B Lagen ("Transmissibility of the common cold exposure of susceptible individuals under controlled conditions" Proc Soc Exper Biol & Med **31** 713 1934) Andrewes (Ref 14) later had a similar experience These observations must mean that virus was inhaled in inadequate dosage that some factor of lowered resistance necessary to potentiate infection was absent or that virus from the donor was already inactive Andrewes (Ref 14) in infected volunteers found virus in nasal washings as long as 24 hours before any symptoms appeared and P H Long, E A Bliss and H M Carpenter ("A note on the communicability of colds Bull Johns Hopkins Hosp **51** 278 1932) in an observation made during an experiment on transmission to monkeys also found that a cold is *transmissible during the incubation period*

14 ANDREWES Christopher Howard Adventures among viruses III The puzzle of the common cold New England J Med **212**:235 1950

In this important summary of the work of the British Common Cold Research Unit Andrewes points out first the difficulties of transmission experiments that the cold cannot be transmitted to small animals or cultivated conveniently in the laboratory Human volunteers are therefore necessary Andrewes describes the complex system of quarantine of the volunteers necessary in transmission experiments He again tells of failures to transmit any disease to a dozen or more varieties of animals—small and large By passing washings through graded filters a virus size of about 0 1 μ is indicated a discouraging fact since small particle viruses are notably unaffected by antibiotics Various other physical characteristics are enumerated Andrewes reminds us that simple exposure to cold will not produce a "cold but he raises the question of whether in certain individuals who may be chronic carriers of cold virus some *types of chilling may not act as a factor which lowers resistance to autoinfection* much as happens with herpes simplex virus carriers Such chronic carriage might explain individuals who are subject to frequent colds when their close associates have none Many more interesting problems in the transmission of colds are discussed

15 POWELL H M SPARKS A L and CLOWES G H A Further inoculation experiments with the common cold virus J Immunol **38** 309 1940

In an attempt to prevent colds the writers administered to volunteers a tissue culture virus by either the hypodermic or the intranasal route They found this *vaccine ineffective in preventing natural colds Dochez and his group* had similar experiences (Ref 11) These findings do not seem remarkable because the spontaneous disease confers so little protection Other failures to protect against colds are those with bacterial vaccines (Use of vaccines for common cold status report of the Council on Pharmacy and Chemistry and the Council on Industrial Health J A M A **126** 895 1944) and with penicillin (C Kuh and M F Collen "Mass penicillin prophylaxis" J A M A **140** 1324 1949)

16 COMMISSION ON ACUTE RESPIRATORY DISEASES Experimental transmission of minor respiratory illness to human volunteers by filter passing agents J Clin Investigation **26** 957 1947

Using bacteria free filtrates of nasopharyngeal secretions of patients with mild acute respiratory infections these workers were able to produce two types of illness One was coryza like with an incubation period of 24–48 hours the other after an incubation period of 5 or 6 days was featured by sore throat and minimal nasal symptoms In another paper the same workers showed (*ibid* p 974) that a specific immunity was conferred by each type and that cross immunity was not demonstrable

17 TOPPING N H Research on the common cold Bull New York Acad Med 25 530 1949

An important review in which the writer points out that the common cold practically heads the list of unsolved problems in respiratory infection

18 BLOOMFIELD Arthur L. Some problems of the common cold J A M.A 144:287 1950

The writer critically reviews the whole subject to date He emphasizes the importance of distinguishing the true common cold—a viral infection—from traumatic rhinitis (*cold dust, fumes allergic reactions psychic*) *with which it is* often confused In either the true cold or traumatic rhinitis there may be secondary bacterial invasion with suppurative complications The literature on prophylaxis and on treatment including antibiotics and "antihistaminics" is also reviewed

19 LOWELL, F C SCHILLER I W ALMAN J E and MOUNTANI C F The antihistaminic drugs in the treatment of the common cold New England J Med 244:132 1951

Histamine had such a vogue in the alleged control of the common cold that this definitive paper should be mentioned "We were unable to distinguish any effect of the three [antihistaminic] drugs in the dosage used on the common cold that differed significantly from the placebo"

20 FINLAND Maxwell Antimicrobial treatment for oral and related infections II Antibiotic treatment of acute respiratory infections and influenza New England J Med 247 557 1952

Finland gives a critical analysis of the value of antibiotics in the prevention and treatment of the common cold He concludes that "none of the antimicrobial agents have been unequivocally demonstrated to have a favorable effect" but that they may prove useful for complications due to ordinary bacteria

21 ANDREWES C H CHAPRONIERE Donna M GOMPELS Annette E H PEREIRA H G and RODEN A T Propagation of common cold virus in tissue cultures Lancet 2 546 1953

Andrewes who had previously failed to grow cold virus in cultures now claimed success by using explants of human embryonic lung in roller tubes modified from the method of J Enders ("Bovine amniotic fluid as tissue culture medium in cultivation of poliomyelitis and other viruses" Proc Soc Exper Biol & Med 82 100 1953) By testing the culture material on human volunteers "evidence is adduced that the common cold virus has been propagated through ten serial cultures of embryonic human lung"

22 HUEBNER R J ROWE W P WARD T G, PARROTT, R H and BELL, J A Adenoidal pharyngeal-conjunctival agents a newly recognized group of common viruses of the respiratory system New England J Med 251:1077 1954

Using the newer methods of tissue culture the writers summarize work of their own and of others in which more than a hundred strains of virus have been demonstrated in material obtained from various mild acute diseases of the upper air passages as well as from surgically removed tonsils and adenoids This work is extremely complex and as yet in an early stage The agents fall into various immunologically separable groups "All types grow readily producing similar and unique cytopathogenic effects in human epithelial cells and in HeLa cells available commercially They are resistant to ether and antibiotics—all types cause frequent infections in man beginning at an early age" On administration of these agents to volunteers no clinical disease was produced but in most of them there was a sharp rise in complement fixing and neutralizing antibody levels and the appearance of virus in nasopharyngeal secretions 3-6 days after inoculation These methods open a new field in the study of viruses of the respiratory passages the exact relation of all this to the true common cold is not yet clear

MEASLES

MEASLES

AN EXCELLENT historical account of measles with bibliography is to be found in J D Rolleston's book on the *History of the Acute Exanthemata* (London William Heinemann 1937) while the modern literature to 1931 is well covered in the "References to Literature" appended to the monograph of David Thomson and Robert Thomson on *Measles* ("Annals of the Pickett Thomson Research Laboratory" Vol 7 [London Baillière Tindall & Cox 1931]) page 193 The most recent literature is reviewed in Babbott and Gordon's *Modern Measles* (Ref 26) Sydenham is usually given credit for distinguishing between measles scarlet fever, and smallpox, and although his accounts were more realistic than the earlier ones they are far from giving a really finished picture of the disease

What impresses one most in the older descriptions of measles is the somewhat different character of the disease from that now seen Whereas there were mild cases there were also many severe outbreaks with high mortality especially from overwhelming bronchopneumonias probably with bacteremia and from gangrene of the face or other structures It is not too hard to see how these fulminating forms with hemorrhagic skin rashes could be confused with similar violent types of scarlet fever and smallpox

1 WILLAN Robert On cutaneous diseases 1 214 London J Johnson 1808

In this monumental book on cutaneous disorders measles is discussed as a skin disease under the chapter on exanthemata The account is vivid in some respects but definitely oriented to the past—to Sydenham and even to the Arabian writers "On the third, fourth or fifth day of the fever when there is oppression with anxiety heaving of the lungs and a labouring pulse most practitioners recommend bloodletting" etc It is evident that early in the century the disease often occurred in very severe form with rapid death from pneumonia or even gangrene

2 GREGORY George Lectures on the eruptive fevers chapter vi "Rubeola or measles" London H Renshaw 1843

Gregory's account is of interest because it is transitional between Sydenham and the moderns An excellent description with consideration of incubation period, prodromes eruption and complications is given He distinguishes measles from scarlet fever "1 By the character and duration of the eruptive fever 2 by the character and general aspect of the eruption 3 by the state of the throat" As to therapy—"On the appearance of the eruption your object is simply to avoid occasions of aggravation Let the patient be confined to bed take occasionally some castor oil and a simple saline draught with syrup of tolu and some antimonial wine every four hours" Gregory goes on with suggestions of mustard plasters leeches and bleeding if "mischief is brewing" in the lungs Of the same general character is the excellent account in F Rilliet and E Barthez (*Traité clinique et pratique des maladies des enfants* [Paris Gearner Baillière 1843] 2 671) A Trousseau (*Clinique médicale de l'Hôtel*

Dieu de Paris [Paris J B Baillière et fils] 1:42) the master clinician gives a good account also but none of these writers was clear as to the duration of the incubation period and none described the enanthem precisely They recognized bronchopneumonia and gangrene as frequent and dreaded complications

3 PANUM P L Iagttagelser anstillede under maeslinge-epidemien paa Faeroerne i Aaret 1846 Bibl laeger I 270 1847 (English translation Observations made during the epidemic of measles on the Faroe Islands in the year 1846 M Classics 3:829 1939)

At the age of only twenty six Panum was sent to the Faroe Islands by the Danish government to investigate a tremendous epidemic of measles during which approximately six thousand of the eight thousand inhabitants were affected The introduction of the disease was brought about by a man who shortly before had been in contact with a measles patient in Copenhagen and who did not become ill until he arrived at Thorshaven the main port of the Faroes His two closest associates then came down, after which the epidemic spread throughout the islands Panum s main contribution was epidemiological he traced the spread of the disease through isolated villages and concluded that there was a latent period between exposure and the outbreak of the rash of exactly 14 (occasionally 13) days The prodromal period varied from 2 to 6 days Panum concluded that the disease was definitely communicable that it was not due to miasm or to spontaneous generation and that it was most con tagious at about the time the rash appeared and not during desquamation as usually supposed He found that isolation was effective in stopping the spread of the disease and he thought that he had evidence that it could be dissemi nated by fomites (clothes) as well as by direct contact Panum also made the interesting observation that old people who had had measles in the previous epidemic in 1781 were not affected The paper begins with an interesting ac count of the geography climate and natural history of the Faroe Islands

Numerous other epidemics of measles have been described the earlier litera ture is reviewed in A Hirsch *Handbook of Geographic and Historical Pathology* (London New Sydenham Society 1883) 1 154 and in Charles Leighton *A History of Epidemics in Britain* (Cambridge 1894) 2 632 Quite recently there is a comprehensive study of an outbreak in Greenland where there had never before been a case of measles (P E Christensen H Schmidt O Jenson H O Bang V Andersen and B Jordal "An epidemic of measles in southern Greenland 1951" Acta med skandinav 144 313 430 450 1952) Almost everyone young and old was affected The incubation period was not so fixed as that found by Panum in one case it was definitely prolonged to 19 days and in several others it was as short as 6–10 days Among 4 257 patients 77 deaths occurred An excellent modern discussion of the epidemiology of measles and of specific epidemics is that of J A H Brincker A historical epidemiological and aetiological study of measles Proc Roy Soc Med 31 807 1938

4 LAVERAN [Alphonse] Des influences nosocomiales sur la marche et la gravité de la rougeole Gaz hebd de méd Paris 8 20 51 1861

Although measles is usually thought of as a childhood disease it becomes wide spread and serious in adults under conditions of assembly of large numbers of soldiers especially of young men from various districts where measles has not

MEASLES

AN EXCELLENT historical account of measles with bibliography is to be found in J D Rolleston's book on the *History of the Acute Exanthemata* (London William Heinemann 1937) while the modern literature to 1931 is well covered in the "References to Literature" appended to the monograph of David Thomson and Robert Thomson on *Measles* ("Annals of the Pickett Thomson Research Laboratory Vol 7 [London Baillière Tindall & Cox 1931]) page 193 The most recent literature is reviewed in Babbott and Gordon's *Modern Measles* (Ref 26) Sydenham is usually given credit for distinguishing between measles scarlet fever and smallpox and although his accounts were more realistic than the earlier ones they are far from giving a really finished picture of the disease

What impresses one most in the older descriptions of measles is the somewhat different character of the disease from that now seen Whereas there were mild cases there were also many severe outbreaks with high mortality especially from overwhelming bronchopneumonias probably with bacteremia and from gangrene of the face or other structures It is not too hard to see how these fulminating forms with hemorrhagic skin rashes could be confused with similar violent types of scarlet fever and smallpox

1 WILLAN Robert On cutaneous diseases 1:214 London J Johnson 1808

In this monumental book on cutaneous disorders measles is discussed as a skin disease under the chapter on exanthemata The account is vivid in some respects but definitely oriented to the past—to Sydenham and even to the Arabian writers "On the third fourth or fifth day of the fever when there is oppression with anxiety heaving of the lungs and a labouring pulse most practitioners recommend bloodletting etc It is evident that early in the century the disease often occurred in very severe form with rapid death from pneumonia or even gangrene

2 GREGORY George Lectures on the eruptive fevers chapter vi Rubeola or measles" London H Renshaw 1843

Gregory's account is of interest because it is transitional between Sydenham and the moderns An excellent description with consideration of incubation period prodromes eruption and complications is given He distinguishes measles from scarlet fever "1 By the character and duration of the eruptive fever 2 by the character and general aspect of the eruption 3 by the state of the throat" As to therapy—"On the appearance of the eruption your object is simply to avoid occasions of aggravation Let the patient be confined to bed take occasionally some castor oil and a simple saline draught with syrup of tolu and some antimonial wine every four hours" Gregory goes on with suggestions of mustard plasters leeches and bleeding if mischief is brewing" in the lungs Of the same general character is the excellent account in F Rilliet and E Barthez (*Traité clinique et pratique des maladies des enfants* [Paris Gearner Baillière 1843] 2 671) A Trousseau (*Clinique médicale de l'Hôtel*

Dieu de Paris [Paris J B Baillière et fils] 1 42) the master clinician gives a good account also but none of these writers was clear as to the duration of the incubation period and none described the enanthem precisely They recognized bronchopneumonia and gangrene as frequent and dreaded complications

3 PANUM P L. Iagttagelser anstillede under maeslinge-epidemien paa Faeroerne i Aaret 1846 Bibl laeger 1:270 1847 (English translation Observations made during the epidemic of measles on the Faroe Islands in the year 1846 M Classics 3 829 1939)

At the age of only twenty six Panum was sent to the Faroe Islands by the Danish government to investigate a tremendous epidemic of measles during which approximately six thousand of the eight thousand inhabitants were affected The introduction of the disease was brought about by a man who shortly before had been in contact with a measles patient in Copenhagen and who did not become ill until he arrived at Thorshaven the main port of the Faroes His two closest associates then came down after which the epidemic spread throughout the islands Panum s main contribution was epidemiological he traced the spread of the disease through isolated villages and concluded that there was a latent period between exposure and the outbreak of the rash of exactly 14 (occasionally 13) days The prodromal period varied from 2 to 6 days Panum concluded that the disease was definitely communicable that it was not due to miasm or to spontaneous generation and that it was most contagious at about the time the rash appeared and not during desquamation as usually supposed He found that isolation was effective in stopping the spread of the disease and he thought that he had evidence that it could be disseminated by fomites (clothes) as well as by direct contact Panum also made the interesting observation that old people who had had measles in the previous epidemic in 1781 were not affected The paper begins with an interesting account of the geography climate and natural history of the Faroe Islands

Numerous other epidemics of measles have been described the earlier literature is reviewed in A Hirsch *Handbook of Geographic and Historical Pathology* (London New Sydenham Society 1883) 1 154 and in Charles Leighton *A History of Epidemics in Britain* (Cambridge 1894) 2 632 Quite recently there is a comprehensive study of an outbreak in Greenland where there had never before been a case of measles (P E Christensen H Schmidt O Jenson H O Bang V Andersen and B Jordal "An epidemic of measles in southern Greenland 1951" Acta med skandinav 144 313 430 450 1952) Almost everyone young and old, was affected The incubation period was not so fixed as that found by Panum in one case it was definitely prolonged to 19 days and in several others it was as short as 6–10 days Among 4 257 patients 77 deaths occurred An excellent modern discussion of the epidemiology of measles and of specific epidemics is that of J A H Brincker "A historical epidemiological and aetiological study of measles" Proc Roy Soc Med 31 807 1938

4 LAVERAN [Alphonse] Des influences nosocomiales sur la marche et la gravité de la rougeole Gaz hebd de méd Paris 8 20 51 1861

Although measles is usually thought of as a childhood disease it becomes widespread and serious in adults under conditions of assembly of large numbers of soldiers especially of young men from various districts where measles has not

been prevalent Laveran who was later to discover the malarial parasite gives a penetrating analysis of measles among troops concentrated in various barracks in France and points out the high incidence of infection in certain years and the high mortality In 1860 for example among 1 000 deaths 116 were due to measles F Prinzing (*Epidemics Resulting from Wars* [Oxford Clarendon Press 1916]) states that during the American Civil War about 75 000 troops contracted measles of whom about 5 000 died (p 179) Prinzing also mentions the high incidence of measles even in old men in the concentration camps during the Boer War (p 293) L Colin ("Note sur la rougeole observée dans l armée de Paris pendant le mois de décembre 1870" Bull Acad de méd Paris 36 6 1871) refers to an outbreak in the Army of Paris in which nearly half of those affected died obviously of secondary bronchopneumonia W Kinnear ("Epidemic of measles in the Highland Division at Bedford 1914-15" Edinburgh M J 30 593 1923) describes a violent outbreak of measles among recruits from the remoter Highlands, in one group there were 139 cases with 21 deaths Measles was also common in the American cantonments during World War I (A W Sellards and E Sturm "The occurrence of the Pfeiffer bacillus in measles" Bull Johns Hopkins Hosp 30 331 1919 E L Opie F G Blake J C Small and T M Rivers *Epidemic Respiratory Disease* [St. Louis C V Mosby Co 1921] chaps v and vi pp 282 334)

5 THOMAS [L] Masern *in* H CURSCHMANN W ZUELZER W HERTZ and H VON ZIEMSSEN Handbuch der acuten Infectionskrankheiten Part II Leipzig F C W Vogel 1874

A detailed discussion modern in tone of every aspect of measles which leaves little to be added The primary disease is clearly distinguished from secondary bronchopneumonia there is full discussion of complications and sequelae such as encephalitis There is an extensive bibliography Thomas also has an excellent description of what were doubtless Koplik s spots (p 66)

6 JURGENSEN Theodor Masern *in* H NOTHNAGEL Specielle Pathologie und Therapie Vol 4, Part 2 Vienna Alfred Holder 1895

An authoritative comprehensive discussion of all phases of the disease

7 KOPLIK Henry The diagnosis of the invasion of measles from a study of the exanthema as it appears on the buccal mucous membrane Arch Pediat 13 918 1896

In this paper Koplik describes the lesion which bears his name On the buccal mucous membrane and the inside of the lips we invariably see a distinct eruption It consists of small irregular spots of a bright red color In the centre of each spot there is noted in strong daylight a minute bluish white speck" Koplik points out that these spots are best seen *before* the eruption and insists that they "are absolutely pathognomonic of beginning measles" and when seen can be relied upon as the forerunner of the skin eruption In a subsequent article ("The new diagnostic spots of measles on the buccal and labial mucous membrane M News 74 673 1899) Koplik complains that his sign has not been adequately recognized in America and he again describes the spots in detail with a beautiful colored plate to illustrate them Meanwhile Slawyk confirmed the occurrence and value of Koplik s spots ("Ueber das von Koplik als Früh

symptom der Masern beschriebene Schleimhautexanthem" Deutsche med Wchnschr 24 269 1898) W R Bett ("Some paediatric eponyms III Koplik's spots" Brit J Child Dis 28 127 1931) critically reviewed the subject and pointed out that others had mentioned the spots but not with the fulness accuracy and tone of conviction of Koplik. Alois Monti ("Studien über das Verhalten der Schleimhaute bei den acuten Exanthemen" Jahrb f Kinderh 6:20 1872) in a comprehensive discussion of the mucous membranes in measles reviews the earlier literature and describes his own careful observations He agrees with previous writers that there is an enanthem usually appearing before the skin rash and affecting diffusely the pharynx larynx palate and buccal cavity He probably saw the same spots as Koplik, which he describes as follows "As to the efflorescences on the gums they are either irregular variously shaped pinhead sized or larger isolated or confluent, red spots or varied sized elevated red papules" He goes on with various details of their appearance Koplik however certainly deserves full credit for forcing the spots on everyone's attention and emphasizing their value in diagnosis before the skin eruption has appeared

8 JOSIAS Albert. Recherches expérimentales sur la transmissibilité de la rougeole aux animaux Méd. mod 9 153 1898

Josias questions the spontaneous occurrence of measles in animals as well as the previous attempts of Behla to transmit the disease to pigs Josias first swabbed the noses and throats of young pigs with mucus freshly obtained from human cases of measles "I will not fatigue the Academy with the details of ten experiments I will limit myself to saying they were all negative" He then turned to monkeys who were treated in similar fashion using in all eight animals Four "macaques" unaffected a "sajou capuchin" and two "sajou robustus" monkeys at intervals of 11–13 days after the swabbing developed fever catarrhal symptoms and a measles like eruption However the descriptions are not altogether convincing as there seemed to be diffuse erythemas not followed by desquamation Our verdict from reading this article is that Josias probably but not certainly produced measles in his monkeys although he is generally credited with having actually accomplished this feat

9 TILISTON Wilder The blood in measles J Infect. Dis 1:551 1904

Although it was noted many years ago that there was absence of leukocytosis in measles in contrast to scarlet fever and indeed actually a leukopenia (S Felsenthal "Haematologische Mittheilungen" Arch f Kinderh 15 78 1893) the paper by Tileston after a review of the literature gives comprehensive studies in twenty-eight cases Tileston pointed out the now well known drop in polymorphonuclear leukocytes toward defervescence with increase of lymphocytes However the careful and comprehensive counts of B Benjamin and S M Ward ("Leucocytic response to measles" Am J Dis Child 44 921 1932) seem definitive In addition to the hematological findings they point out changes in the lymph nodes

10 HEKTOEN Ludvig Experimental measles J Infect Dis 2 238 1905

Hektoen reviews the literature on attempts deliberately to transmit measles to man and points out that this was tried for the most part not for scientific

reasons but as a practical attempt to produce an immunity to the disease by transmitting a mild attack after the manner of smallpox inoculation Practically all these attempts are to be criticized because either the disease produced was atypical and doubtful or because spontaneous infection was not excluded. Nasal secretions blood and skin scrapings were all tried as a source of "virus" and inoculations were usually made into skin cuts or occasionally into the upper air passages Hektoen reports two transmission experiments of his own which he considers successful In his second case blood was drawn from a patient with measles about 30 hours after appearance of the rash and was incubated in flasks of ascites broth After 24 hours 5 cc were injected subcutaneously into a twenty eight year old man in whom spontaneous infection was definitely excluded On the eleventh day the temperature began rising and reached 103 F on the thirteenth day with the appearance of a typical rubeolous rash Hektoen later again comprehensively reviewed the subject ("Experimental measles" J A M A 72 177 1919)

11 CENCI F Alcune esperienze di sieroimmunizzazione e sieroterapia nel *morbillo Riv clin pediat*, 5 1017, 1907

Cenci was apparently the first to report on the use of convalescent measles serum as a prophylactic against the disease None of four children who received injections contracted measles although repeatedly exposed However these children over a year later when exposed again took the disease which showed that the passive protection is brief

In spite of these definite observations of Cenci credit for introducing passive prophylaxis is usually given to Nicolle and Conseil (Ref 15)

12 EWING James The epithelial cell changes in measles J Infect Dis 6 1 1909

Ewing reviews the early and confused reports on the histology of measles lesions and describes his own results with material obtained at post mortem and in tissues taken from three patients during life Ewing concludes that the "wide spread occurrence of very acute degeneration and necrosis of epithelial cells all suggest that measles is referable to infection by a bacterium" Today the changes described would undoubtedly be thought characteristic of a virus F B Mallory and E M Medlar ("The skin lesion in measles" J M Research 41 327 1920) made a thorough histological study of bits of skin excised during measles The absence of the polymorphonuclear reaction was striking there was proliferation of endothelial cells in the capillaries and necrosis of epithelium Obscure bodies are described in the swollen endothelial cells lining the capillaries which may have been "inclusion bodies" athough the authors do not make this suggestion but regard them as phagocyted cocci in various stages of dissolution Still later Warthin (Aldred Scott Warthin "Occurrence of numerous large giant cells in the tonsil and pharyngeal mucosa in the prodromal stages of measles Arch Path 11 864 1931) described a lesion which he regarded as specific of measles "a subepithelial infiltration of multinucleate syncitial giant cells lymphocytes and monocytes" W Finkeldey ("Ueber Riesenzellbefunde in den Gaummenmandeln zugleich ein Beitrag zur Histopathologie der Mandelveranderungen im Maserninkubationsstadium" Virchows Arch f path Anat 281 321 1931) described similar giant cells

13 ANDERSON John F and GOLDBERGER Joseph Experimental measles in the monkey a preliminary note Pub Health Rep 26:847 1911

The writers were apparently not familiar at first with the previous work of Josias (Ref 8) They used blood drawn from measles patients to inoculate (route not stated) rhesus monkeys Slight rises in temperature were obtained after incubation periods of 8–10 days with variable maculopapular eruptions over face and body lasting a few days In a later paper ("Experimental measles in the monkey a supplemental note" *ibid* p 887) the writers give details of their experiments The blood drawn from the donors early in the disease was defibrinated and from 0 5 to 10 cc were injected intraperitoneally in monkeys In two instances intracerebral injections were given The results as to both incubation period and eruption are suggestive They also thought that they had produced measles with blood drawn from inoculated monkeys Anderson and Goldberger reported that only two of nine monkeys gave a clearly marked reaction which they thought was due to "a low degree of susceptibility of the monkey" In another paper ("The period of infectivity of the blood in measles" J A M A 57:113 1911) the same authors found that blood drawn before and early in the exanthem gave positive reactions in monkeys whereas blood drawn after first appearance of the rash gave no reaction Soon after Goldberger and Anderson ("An experimental demonstration of the presence of the virus of measles in the mixed buccal and nasal secretions" *ibid* p 476) turned their attention to the secretions of the upper air passages as a source of infection They first exposed a young Java monkey to monkeys with "experimental measles After a time he developed a fever and an eruption Subsequently mixed buccal and nasal secretions from patients in the early stages of measles were swabbed in the throats of monkeys and also given subcutaneously In some cases it was thought that measles was produced Still later Goldberger and Anderson ("The nature of the virus of measles" *ibid* p 971) reported on the characteristics of the virus which they thought passed a Berkefeld filter resisted desiccation for 25½ hours and lost its infectivity after heating at 55 C for 15 minutes A scrutiny of all these experiments shows results so irregular in time and in the clinical phenomena that one is forced to believe that while the writers possibly produced measles one cannot be absolutely certain for example in one animal the eruption appeared 21 days after inoculation in others there were febrile reactions without rash etc

Meanwhile Albert S Grunbaum ("Some experiments on enterica scarlet fever and measles in the chimpanzee" Brit M J 1:817 1904) in two experiments admittedly incomplete did not succeed in transmitting measles by swabbing nasal secretions in the nose and throat of the monkey But Ch Nicolle and E Conseil (Reproduction expérimentale de la rougeole chez le Bonnet chinois Virulence du sang des malades 24 heures avant le début de léruption" Compt rend Acad d sc 153 1522 1911) accepted Anderson and Goldberger s work and reported an experiment of their own They introduced intraperitoneally into a *Macacus sinicus* 6 cc of blood drawn from a child 24 hours before the eruption appeared The monkey developed a fever on the sixth day which slowly rose until the twelfth day and then receded No mention is made of an eruption Ludvig Hektoen and E H Eggers (Experi

mental measles in the monkey with special reference to the leukocytes" J A M A 57 1833 1911) also thought that they had confirmed Anderson and Goldberger s work and furthermore described changes in the blood leukocyte count which seemed analogous to those of human measles W P Lucas and E L Prizer (An experimental study of measles in monkeys J M Research 26 181 1912) in transmission experiments to monkeys (rhesus) obtained find ings similar to those of previous workers including leukopenia but they also described Koplik s spots in the experimental disease They passed the "disease" through several monkeys Finally Hektoen ("Experimental measles J A M A 72 177 1919) reviewed the entire subject to date in thorough fashion. He con cluded that the disease had been reproduced in *monkeys only* but that it was usually mild and atypical, although definite "The results in monkeys show that the cause of measles is present in the naso pharyngeal secretions and the blood at least twenty four hours before the rash as well as for a day or two afterward"

One of the *few voices which have questioned the validity of these transmis* sion experiments was that of Sellards whose critique is well worth reading even *today when experimental transmission is unquestioned* (A W Sellards A re view of investigations concerning the etiology of measles" Medicine 3 99 1924)

14 COLE Rufus and MacCALLUM W G Pneumonia at a base hospital J A M A 70 1146 1918

Classical studies of pneumonia following measles at a base hospital MacCallum gives a clear description of interstitial (viral) pneumonia but attributes it to *S hemolyticus* which was surely a secondary invader

15 NICOLLE Charles and CONSEIL E Pouvoir préventif du serum d un malade convalescent de rougeole Bull et mém Soc Méd d hôp de Paris 2 336 1918

Three of four children in a family had successively come down with measles The fourth received an injection of serum from a convalescent brother He re mained well thus confirming the work of Cenci (Ref 11) Shortly thereafter D L Richardson and Hilary Connor (Immunization against measles" J A M A 72 1046 1919) attempted immunization by injections of convales cent serum and by injection of serum together with "virus By the latter pro cedure they treated three children in only one of whom was there a slight reac tion featured by a transient rise in temperature and an atypical rash Rudolf Degwitz ("Ueber Versuche mit Masernrekonvaleszentenserum" Ztschr f Kinderh 25 134 1920) treated a considerable number of children with pro phylactic injections of convalescent measles serum none developed measles whereas uninjected controls came down Degwitz soon elaborated these studies (Ueber Masern Reconvaleszentenserum *ibid* 27 171 1920) and pointed out that to confer secure protection the serum must be given by the sixth day of the incubation period A little later Rietschel ("Zur *Masernprophylaxie nach* Degwitz, Ztschr f Kinderh 29 127 1921) pointed out that serum from the mother i e from any adult who had had measles was effective in protecting M Stillerman H H Marks and W Thalhimer ("Prophylaxis of measles with convalescent serum" Am J Dis Child 67 1 1944) reviewed the whole sub ject to date Finally C F McKhann and Fu Tang Chu ("Use of placental ex

tract in prevention and modification of measles" Am J Dis Child 45:475 1933) noting reports on prophylaxis of measles with blood from umbilical cord and placenta prepared a placental extract which given intramuscularly early in the incubation period conferred protection against or at least attenuation of the attack of measles

16 HEKTOEN Ludvig The bacteriology of measles J.A M A 71 1201 1918

Measles as well as most other infectious diseases was at one time or another blamed on all sorts of bacteria The numerous claims are critically reviewed by Hektoen Although he does not fully clarify the situation there is an attempt to separate secondary invaders from the primary cause The subject is also critically reviewed by J E McCartney "A review of recent work on measles" Lancet 1:93 1927

17 BLAKE Francis G and TRASK James D Jr Studies on measles I Susceptibility of monkeys to the virus of measles J Exper Med 33:385 1921

After questioning previous work on transmission of measles to monkeys Blake and Trask reported experiments of their own in which nasopharyngeal washings from patients were instilled intratracheally into monkeys (*Macacus rhesus*) They concluded that they had produced measles and had transmitted the dis ease from monkey to monkey In a second paper ("Studies on measles II Symptomatology and pathology in monkeys experimentally infected" *ibid* p 413) Blake and Trask described the clinical course and the microscopic lesions "The symptoms and course of this reaction closely parallel those of human measles" The lesions of the skin and buccal mucous membranes "are essen tially identical with the corresponding lesions of measles in man"

18 HERRMANN Charles The relative immunity of infants under five months of age to infection with measles Arch Pediat 40 678 1923

The writer gives statistics showing that infants up to two months old are im mune to measles that they possess a partial resistance up to six or seven months and that thereafter practically all acquire the disease if exposed This resistance Herrmann believes due to protective substances transmitted from the mother via the placental circulation

19 FORD F R The nervous complications of measles Bull Johns Hopkins Hosp 43 140 1928

This is an elaborate and definitive article on the nervous complications of measles Ford abstracts reports of 113 cases from the literature and adds 12 of his own The onset is usually on the fourth to sixth day and the great variety of neurological symptoms is emphasized The spinal fluid cell count may reach 200 or more The pathological anatomical process is that of a toxic-degenerative rather than an inflammatory process Only about 10 per cent of all patients die but about 65 per cent of those who survive show residual symptoms The liter ature is reviewed

20 PLOTZ Harry Culture "in vitro du virus de la rougeole Bull Acad d méd Paris 119 598 1938

Plotz placed blood from a patient with measles in flasks of a special medium containing chick embryo hash Five cubic centimeters of this material from the tenth passage injected subcutaneously produced frank mea les in a monkey We think then that we can conclude that we have grown the measles virus in culture" G Rake M F Shaffer and H P Jones (Studies on measles III The use of tissue culture in the propagation of measles virus" J Infect Dis 69 65 1941) review the attempts at tissue culture by various workers and repeat and confirm Plotz s work

21 RAKE, Geoffrey and SHAFFER Morris F *Studies on measles I The use of the chorio-allantois of the developing chicken embryo* J Immunol 38 177 1940

The writers criticize previous attempts to grow measles virus in fertile hen s egg such as those of G K Wenckebach and H Kunert ("Die Zuchtung des Masernvirus" Deutsche med Wchnschr 63 1006 1937) and report experiments of their own The agent of measles obtained from the blood or pharyngeal washings of human cases has been propagated by serial passage on the chorio allantois of the fertile hen s egg in the absence of macroscopic lesions The presence of the agent has been demonstrated by the inoculation of pooled chorio allantois and viscera of the chick embryos into monkeys (*Macacus mulatto*) with the production of a disease indistinguishable from that brought about by the injection of material obtained from cases of human measles From monkeys infected with material from either source measles virus can again be propagated in the fertile hen s egg"

22 SHAFFER Morris F RAKE Geoffrey STOKES Joseph Jr and O NEIL Gerald C *Studies on measles II Experimental disease in man and monkeys* J Immunol 41 241 1941

The writers try to resolve the doubts of some that the experimental disease is really measles They simultaneously inoculated some children and monkeys subcutaneously with pooled blood from measles cases and others with chicken embryo passage virus In both children and monkeys enough reactions consisting of fever coryza Koplik s spots leukopenia and rash occurred to convince them that the disease was actually measles However only four of thirty six children who received the egg passage virus developed mild but definite measles J Stokes Jr G C O'Neil M F Shaffer G Rake and E P Maris ("Studies in measles IV Results following inoculations of children with egg passage measles virus" J Pediat 22 1 1943) continued these studies They inoculated a large number of children with egg passage virus and produced measles but in a mild attenuated form in the majority Human passage did not restore the virulence of the virus Forty of forty six children who had had the experimental disease were immune on exposure or reinoculation which suggested to the writers that active immunization with the mild experimental disease might be useful as prophylaxis of severe measles (Studies on measles V The results of chance and planned exposure to unmodified measles virus in children previously inoculated with egg passage measles virus *ibid* p 17) Rake ("Experimental investigations of measles" J Pediat 23 376 1943) later summarized all his experiments

23 STOKES J Jr MARIS E I and GELLIS S S XI The use of concentrated normal human serum gamma globulin (human immune serum globulin) in the prophylaxis and treatment of measles J Clin Investigation 23:531 1944

These were the first workers to report on the use of "gamma globulin" in measles Exposed children who received the serum were almost always protected whereas in those to whom it was given after Koplik s spots or rash were present the disease seemed to be modified in a considerable number At the same time C W Ordman C G Jennings Jr and C H Janeway ("XII The use of concentrated normal human serum gamma globulin [human immune serum globulin] in the prevention and attenuation of measles" J Clin Investigation 23 541 1944) found that in an exposed group gamma globulin injections afforded a rate of 71 per cent protection 27 per cent modification and only 2 per cent failure among sixty two inoculated children A dose of 0 1 cc per pound of body weight within the first 5 days after exposure appeared adequate as a rule

24 REAGAN R L HARMON M DAY W and BRUECKNER A L Electron microscope studies of the virus of measles (Morbilli) Texas Rep Biol & Med 10 655 1952

Studies by electron microscopy of serum of monkeys infected with the virus of measles show the virus to be round The virus particles have a diameter of 90 to 100 mμ These bodies could not be demonstrated in normal monkey serum subjected to the same procedure The virus in concentrated material was infectious for susceptible monkeys but had no effect on monkeys previously immunized against measles with immune serum globulin" There is an illustration of the virus particle × 130 000

25 ENDERS John F and PEEBLES Thomas C Propagation in tissue cultures of cytopathogenic agent from patients with measles Proc Soc Exper Biol & Med 86 277 1954

Since the work of Rake there had been little progress in isolation of measles virus Rake s infected tissue cultures showed no visible changes and had to be tested by the awkward method of monkey inoculation Enders and Peebles apparently succeeded in isolating a virus in cultures of human or monkey kidney cells which produced visible cytopathogenic effects "Primarily these changes consist in the formation of syncitial giant cells" not unlike those described in man by Warthin (Ref 12) These effects could be inhibited by convalescent measles sera "Antigen appears during cultivation *in vitro* of the measles agent that reacts specifically in complement fixation tests with convalescent phase measles sera"

26 BABBOTT Frank L Jr and GORDON John E Modern measles Am J M Sc 228 334 1954

An extensive critical review with literature of all phases of the disease

SMALLPOX

Clinical	Ref 2
Complement fixation	Ref 8
Diagnostic procedures	Refs 8 9 13
General	Ref 1
Growth of virus in chick embryo	Ref 12
Guarnieri bodies	Ref 3
Immunity	Ref 14
Leukocytes	Ref 4
Paschen bodies	Ref 7
Pathology	Ref 5
Paul test	Ref 9
Smallpox inoculation	Ref 1
Smallpox in the monkey	Ref 6
Statistics	Ref 11
Viremia	Ref 14

Section 25

SMALLPOX

BIBLIOGRAPHIES of smallpox are to be found in G Jochmann s *Pocken und Vaccinationslehre* (Vienna Alfred Holder 1913) in F R Blaxall s valuable article on smallpox in *A System of Bacteriology in Relation to Medicine* (London His Majesty s Stationery Office 1930), 7 84 ff following the article on smallpox in *Virus Diseases of Man* by C E Van Rooyen and A J Rhodes (New York Thomas Nelson & Sons 1948) pages 404 ff in the article by J E Smadel in T M Rivers *Virus and Rickettsial Infections of Man* (2d ed Philadelphia J B Lippincott & Co 1952) page 414 and in the recent book by Harvey Blank and Geoffrey Rake *Viral and Rickettsial Diseases of the Skin Eye and Mucous Membranes of Man* (Boston Little Brown & Co, 1955) All these reference lists deal with both smallpox and vaccinia but the present section of this bibliography is limited to consideration of smallpox vaccinia will be dealt with separately

The superficial manifestations of smallpox are so picturesque that it is small wonder that the disease is one of great antiquity associated with popular legend and folklore Nonetheless smallpox appears often to have been confused with other disorders especially measles perhaps for the following reasons The early erythematous lesions may be difficult to interpret and in many severe cases a hemorrhagic rash was associated with death before the typical eruption appeared This in turn was at times masked by secondary infection with general sepsis and pneumonia. Neglect and unhygienic surroundings might further modify the picture To Sydenham is often ascribed the first clear definition of *the smallpox* but while his account is recognizable it is so buried under an accretion of inconsequential material and humoral doctrine as to be of little more than historical interest This sort comes forth sometimes like an erysipelas sometimes like the measles and as to outward appearance they cannot be distinguish d by any but those that are very conversant in this Disease " (Thomas Sydenham *The Whole Works* etc [4th ed London R Wellington 1705] p 82) Nearly one hundred years later Huxham a great authority seems even more primitive "For first when the variolous Contagion attacks a Person of strong tense Fibres and a rich dense Blood commonly a smart inflammatory Fever comes in which sometimes the Lungs sometimes the *Brain the Throat and other Parts are greatly inflamed and on Bleeding* you have a very thick inflammatory Blood (John Huxham *An Essay on Fevers* [4th ed London J Hinton 1794] p 126) By 1811 E G Clarke (*The New London Practice of Physic* [7th ed London Longman Hurst Rees & Orme 1811] p 71) was able to give an excellent account although his discussion of therapy dominated by the doctrine of humors is still primitive If the disease should seize people whose constitution labours under an inflammatory diathesis and has the symptoms of an old inflammatory fever copious bleeding is necessary " etc

The history of smallpox has been elaborately dealt with and those wishing to pursue it further are referred to the following works James Moore *The History of the Small Pox* (London Longman Hurst Rees & Orme 1815)

Charles Creighton *A History of Epidemics in Great Britain* (Cambridge Cambridge University Press 1891) Vol 1, chap ix and Vol 2, chap iv J D Rolleston *The History of the Acute Exanthemata* (London William Heinemann 1937) August Hirsch *Handbuch der historisch-geographischen Pathologie* (2d ed Stuttgart Ferdinand Enke 1881) 1 88 ff (in English translation [London New Sydenham Society 1883] 1 123) That smallpox was communicable was known at least in the seventeenth century and probably earlier It was this knowledge and the belief that one attack conveyed immunity that led to the practice of purposeful inoculation with material from smallpox lesions in order to confer protection by producing what one hoped would be a mild form of the disease The history of this phase of the subject is of immense interest but does not seem appropriate to this bibliography since inoculation was generally abandoned in the early part of the nineteenth century There was however a bitter controversy between those who continued to favor inoculation rather than Jennerian vaccination (cowpox) to which appropriate allusion will be made The history of inoculation with reference to original sources is comprehensively given in Edward J Edwardes *A Concise History of Small Pox and Vaccination in Europe* (London H K Lewis 1902) page 24 and in Crookshank s elaborate *History and Pathology of Vaccination* (London H K Lewis 1889) Vol 1, chaps 1-3 An especially readable account is to be found in Sir James Moore s book (*op cit* chap viii pp 218 ff) The procedure was evidently one of great antiquity in the Orient The Chinese are said to have taken "a few dried Small Pox crusts as if they were seeds and planted them in the nose" (p 219) "with the vain hope of mitigating their acrimony they were sometimes kept in closed jars for years" (p 219) "But at the beginning of the eighteenth century there was communicated to the Royal Society of London a discovery to which the Faculty can lay no claim and as it was first brought to England from Constantinople it was at first named the Byzantine operation although certainly not invented there" (p 218) "The operation was variously performed and on different parts of the body but it always consisted in scratching or puncturing the skin and inserting into the wound variolous matter (p 224) Although several physicians wrote about the practice in English as early as 1715 "no Englishman ever thought of trying it But soon afterward it accidentally happened that Lady Mary Wortley Montague then blooming in beauty traveled into Turkey with her husband the ambassador to the Ottoman Court in her train" Lady Mary in one of the celebrated letters which she wrote home (*Letters of the Right Honourable Lady M—y W—y M—e Written during Her Travels in Europe Asia and Africa* Letter XXXI [various eds])[1] tells about the practice by which the children were hardly made ill and there was no example of any one dying" She therefore had her own son successfully "ingrafted" On her return to England her daughter was inoculated by Mr Maitland with good results Lady Mary actually effected a complete revolution in the practice of Small Pox all over Europe"

Caroline princess of Wales was now desirous of having her children receive the new treatment But not venturing to rely solely upon the medical skill of Lady Mary Wortley Montague Her Royal Highness obtained from George

[1] This letter has so often been reprinted that we shall not take space to do so here

the First that six condemned felons should be pardoned for the good of the public on condition of their submitting to be inoculated" (p 229) Neither the legality nor the morality of this unprecedented act were questioned and still less did the criminals demur but an unlooked for obstacle occurred the surgeon refused to perform the operation for notwithstanding his former success he dreaded a failure and of being stigmatized for doing the work of the executioner" However the felons were finally inoculated five contracted small pox and all escaped hanging This success encouraged Mr Maitland to treat still others The Princess of Wales was now eager to begin but before going ahead the procedure was tried on eleven charity children of St James Parish who all did well Sir Hans Sloane was now consulted on the propriety of treating the princesses but he was cautious about taking responsibility and a long argument ensued Finally the two princesses Amelia and Carolina, were inoculated and the smallpox proved of a benign sort"

For the next hundred years the merits of inoculation were hotly debated *not uncommonly severe or fatal smallpox was produced* and a number of epidemics were initiated However it was Jennerian vaccination which finally supplanted inoculation although much was learned about smallpox and about immunity from the practice A vast amount was early written on the subject *there may be mentioned as especially interesting the book of Baron* T Dimsdale *Tracts on Inoculation Written and Published at St Petersburg in the Year 1768 by Command of Her Imperial Majesty the Empress of All the Russias* (London James Phillips 1781) and the little treatise of Alexander Munro *An Account of the Inoculation of Small Pox in Scotland* (Edinburgh Drummond 1765) which contains valuable mortality statistics of the procedure It is of interest that one of the standard arguments against inoculation was that one was flying in the face of providence by interfering with the natural course of disease

I TROUSSEAU A Clinique médicale de l'Hôtel Dieu de Paris 1 60 article "Variole" Paris J B Baillière et fils *1861*

It is next to impossible to decide who wrote the first adequate description of smallpox At any rate the detailed and graphic account by the master clinician Trousseau based on accurate personal observation of patients has been we believe surpassed by no one He divides smallpox into the "discrete" cases *usually benign and the confluent cases often fatal Of the former he says* "The periods which it runs through are easy to distinguish They are the period of invasion the period of eruption the period of maturation or of suppuration the period of desiccation" The manifestations of the disease "are precisely characterized and it is not possible to confuse them even with those of chicken pox an essentially different disease It is important above all to distinguish the two principal forms because the discrete smallpox is ordinarily exempt from danger Confluent smallpox on the other hand is a terrible disease and everyone knows how rarely it spares those whom it strikes down"

There follows a vivid and precise description of the various stages often illustrated by examples of individual cases "You will recall in this connection the patient whom you saw in Bed No 9 in the St Agnes Ward etc"

In connection with the severe confluent forms secondary infection is empha

sized "What is terrible about small pox is not only that it kills in the acute phase but that it kills even when it so to speak has made its retreat and when the danger seems to have passed it kills by the severe suppurations of which we have spoken suppurations invading the tissues of the limbs the serous membranes pneumonia which goes on quickly to suppuration" Anasarca albuminuria and hematuria are discussed as complications of the confluent forms

That Trousseau wrote in a modern critical spirit is nowhere better shown than in the remarks on treatment "This paragraph will necessarily be brief because with the eruptive fevers there is rarely a chance for medicine to intervene effectively These diseases run a natural course one will be content to prescribe refreshing drinks" and general nursing care This is in sharp contrast to the "eye of newt and toe of frog" prescriptions of a generation previously

Of an excellence comparable to Trousseau s is the account by J F Marson in Reynolds *System of Medicine* (Philadelphia J B Lippincott & Co 1866) 1: 223 The best modern description comprehensive and precise is that of Jochmann in his textbook of infectious disease (G Jochmann *Lehrbuch der Infectionskrankheiten* [Berlin Julius Springer 1914] p 799) and also that in his larger treatise *Pocken und Vaccinationslehre* The article by Smadel in Rivers *Viral and Rickettsial Infections of Man* page 414 places emphasis not only on clinical description but on modern aspects of smallpox virus as does the account in the book by C E Van Rooyen and A J Rhodes (*op cit*)

2 GUARNIERI G Recerche sulla pathogenesi ed etiologia dell infezione vaccinica e variolosa Arch per le sc med 16 403 1893 (German abstract Ueber die Parasiten der Variola und der Vaccine Centralbl f Bact 16 299 1894)

In histological studies of smallpox Guarnieri described the inclusion bodies which bear his name and are well known today A less clearly remembered facet of the story is that Guarnieri regarded these bodies as parasites which were the cause of the disease and he assigned to them the name of *Cytoryctes vaccinlae* resp *variolae* To these "organisms" he ascribed an ameboid movement when observed in hanging-drop preparations of material from smallpox vesicles and he also convinced himself that he saw them undergo multiplication Guarnieri was evidently strongly influenced by the studies on malarial Protozoa which were then being actively pursued in Italy Guarnieri interestingly enough was almost universally believed, and a huge literature of confirmatory reports grew up with only a few dissenting voices[2] It would serve no purpose to review the literature as this has been thoroughly done by Councilman Magrath and Brinckerhoff (Ref 4) It is of interest that as astute and careful an observer as Councilman fully accepted Guarnieri s views ten years later In a brief paper (W T Councilman G B Magrath and W R Brinckerhoff "A preliminary communication on the etiology of variola" J M

[2] But see for example P Muhlens and M Hartmann ("Zur Kentniss des Vaccineerregers Centralbl f Bact 41 41 203 338 435 1906) who after an elaborate study conclude "The Guarnieri bodies are products of a regressive metamorphosis of the nuclear substance of the epithelial cells"

Research 9 372 1903) it is stated The bodies in the cells we regard as living organisms and the gradual growth and final segmentation as a cycle in its life history At the period of segmentation small round or oval ring like bodies appear in the nucleus Dr Tyzzer working with inoculated rabbits and calves found similar bodies and the complete cycle of this organism which corresponds to the primary cycle of the smallpox organism has been traced In variola the entire process of development of the parasite is concluded with the formation of the young vesicle The spores are present in the contents" The bodies are beautifully pictured in Councilman s longer article (Ref 4) and by Gary Calkins ("The life history of Cytoryctes variolae Guarnieri J M Research 11 136 1904) who traces in detail and elaborately illustrates the cycle of the supposed parasite

Thus we have the counterpart of what has happened in the history of nearly every infectious disease the *Bacillus malariae* of Klebs and Tommasi Crudeli the globoid bodies of poliomyelitis Noguchi s leptospira of yellow fever and innumerable others all had their vogue as the cause of one or another disease In Osler s *Principles and Practice of Medicine* smallpox is still classified under diseases of doubtful etiology in the twelfth edition (1935) and under the heading "Nature of the infection it is still stated that "Protozoon like bodies were described in the skin lesions by Guarnieri Cytoryctes variolae" It was not until the thirteenth edition (1938) that smallpox was classified under virus diseases although the statement about *Cytoryctes variolae* is still preserved

3 MAGRATH G B BRINCKERHOFF W R and BANCROFT I R The leucocyte reaction in variola J M Research 11 247 1904

The writers review the early literature and find that the first adequate observations on the subject were those of Jules Courmont and V Montgard (La Leukocytose dans la variole J de physiol et de path gén 2 557 1900) who in a comprehensive study found that there was always a leukocytosis beginning early before vesiculation and consisting of an increase in mono nuclears whereas polymorphonuclears were relatively diminished Alexander R Ferguson ("The leucocytosis of variola" J Path & Bact 8 411 1903) reported similar findings He made daily counts and found the peak of the leukocytosis on or about the ninth day of the disease Magrath and his associates elaborated these studies still further They concluded that the leukocytosis of variola owed its characteristic feature "to the failure of the haemato poietic organs to produce the adult cells called for They found degenerative phenomena in the polymorphonuclears in severe cases which they regarded as due to accentuation of the process of leukocyte destruction Finally Kano Ikeda (The blood in purpuric small pox J A M A 84 1807 1925) in twelve cases of purpuric smallpox found in addition to the changes in the leukocytes a marked thrombocytopenia

As to the bone marrow this seems first to have been studied by C Golgi (Sulla alterazioni del midollo delle ossa nel vajuolo Osservatore Torino 9 161 1873) Golgi found that in hemorrhagic variola aside from hemor rhages there was diminution in the number of leukocytes and increase in nucleated red cells whereas with pustular variola there was an increase in leukocytes and "giant cells H Chiari ("Ueber Osteomyelitis variolosa"

Beitr z path Anat u z. allg Path 13:13 1893) described what he thought was a specific variolous lesion in the bone marrow in the form of disseminated focal lesions H Roger O Josué and Émile Weil ("La Moelle osseuse dans la variole" Arch de méd expér et d anat. path 12:545 1900) later correlated the appearance of the bone marrow with the peripheral blood count

4 COUNCILMAN W T MAGRATH G B and BRINCKERHOFF W R The pathological anatomy and histology of variola J M Research 11:12 1904

Councilman and his associates in the Boston epidemic of smallpox of 1901–2 made meticulous gross and microscopic examination of smallpox lesions in fifty four autopsies In reviewing the literature they attributed the first adequate anatomical studies to Carl Weigert (*Anatomische Beitrage zur Lehre von den Pocken* [Breslau Max Cohen & Weigert 1874]) Weigert basing his studies on two hundred cases examined during the Breslau epidemic of 1871–72 confined his description to the skin lesions (*die Pocken-Efflorescenzen der ausseren Haut*) He concluded that the changes were neurotic and irritative and that the bacteria regularly seen were either the carriers of the infectious material or the material itself Weigert published reproductions of the histological changes A little later P G Unna ("Ueber den Sitz der Pocken in der Epidermis und die ersten Studien des Pockenprocess" Virchows Arch f path Anat 69 409 1877) gave a careful description of the skin lesions with illustrative plates Councilman s monograph is however in a sense definitive He and his associates described not only the skin lesions but those of the mucous membranes and of the various viscera They give numerous beautiful plates of the histological changes and they conclude that "the specific [skin] lesion of variola is a focal degeneration of stratified epithelium vacuolar in character and accompanied by serous exudation and the formation of a reticulum The fully developed product of these processes is a characteristic multilocular pock or pustule" The visceral lesions on the other hand, seemed largely non specific although all sorts of degenerative changes are described as for example those in the liver (H Roger and M Garnier "Étude anatomique et chimique du foie dans la variole" Arch méd expér 13 661 1901) In summary Councilman divided the lesions into (A) the specific limited to stratified epithelium of skin and of the mucous membranes of the soft palate the pharynx and the esophagus (B) associated lesions of indeterminate specificity such as degenerative and cellular infiltrative with mononuclear basophilic elements and (C) associated lesions bacterial in origin It is of interest that Councilman mentioned interstitial changes in the bronchopneumonic pulmonary lesions

5 MAGRATH G B and BRINCKERHOFF W R On experimental variola in the monkey J M Research 11 230 1904

The writers attribute the first report of successful monkey inoculation to W Zuelzer ("Zur Aetiologie der Variola" Centralbl f d. med Wissensch 12 82 1874) An inspection of this article leaves one in doubt however as to whether Zuelzer was really successful Magrath and Brinckerhoff produced the typical disease in monkeys by inoculation of virus into the skin the reaction however was very mild They concluded that variola virus can be transferred from a

man to a monkey from the monkey to the rabbit s cornea through four genera tions and when then inoculated on the monkey can produce a protopustule followed by a general exanthem

6 PASCHEN E Was wissen wir uber den Vakzineerreger? Munchen med Wchnschr 53 2391 1906

Guarnieri bodies are to be sharply differentiated from those to which Paschen s name has become attached The latter are minute granules demonstrable in material from vaccinia variola and alastrim It has been claimed that they were first described by J B Buist ("The life history of the microorganisms associated with variola and vaccina" Proc Roy Soc Edinburgh 13 603 1886) but study of his report leaves one doubtful as to what he actually saw and credit is usually given to Paschen for discovering them Convinced that the organisms of smallpox must be present in huge numbers in the lymph of vesicles Paschen studied smears of diluted material with all sorts of stains

Microscopic examination of these preparations showed a surprisingly large number of uniformly stained very small bodies" These he divided into four types or stages "Are we dealing with developmental stages or with a strange organism or with simple nuclear precipitates? I simply record these findings without drawing any conclusions" The paper is a landmark and includes a careful review of previous work on experimental vaccinia and on previous attempts to demonstrate the etiological agent It is now believed that the Paschen bodies are identical with the elementary bodies known to be the virus of smallpox

For an authoritative review of the subject to date the reader is referred to the article by J E Smadel and C L Hoagland Elementary bodies of vaccinia Bact Rev 6:79 1942 as well as chapter 29 "The variola vaccinia virus elementary and inclusion bodies in Van Rooyen and Rhodes *op cit* C E Van Rooyen and R S Illingworth ("A laboratory test for diagnosis of small pox Brit M J 2 526 1944) impressed by the need of an early diag nostic test for smallpox utilized the fact that the "elementary bodies of variola are larger than those of varicella Scrapings from the base of early lesions were stained by special techniques The laboratory and clinical findings corresponded in 96 per cent of the cases

7 GORDON M H Studies of the viruses of vaccinia and variola p 108 (Medical Research Council Special Reports Series" No 98) London His Majesty s Stationery Office 1925

Gordon applied the complement fixation technique to the diagnosis of small pox, using a suspension of variola scabs as antigen R F Parker and R S Muckenfuss ("Complement fixation in vaccinia and in variola" J Infect Dis 53 44 1933) critically reviewed the subject and described a technique of their own using a specific antivaccinial serum and fluid from the pustules The subject was further developed by Craigie and Wishart (Ref 11)

8 TOOMY John A and GAMMEL John A The Paul test in the diagnosis of small pox, J Infect Dis 41 29 1927

Guarnieri (Ref 2) inoculated the corneas of rabbits with smallpox material and demonstrated that a lesion resulted Others including Juergens ("Descrip-

tion of microscopic preparations" Berl klin Wchnschr 42:308 1905) further emphasized the peculiar proliferations of the corneal epithelium which followed inoculation with smallpox material Gustav Paul ("Eine neue Untersuchungsmethode der variolierten Hornhaut des Kaninchenauges zur objektiven Sicherung der Varioladiagnose" Wien klin Wchnschr 29:996 1916) however first emphasized the possibility of using the appearance of the variolated cornea as a specific diagnostic test for smallpox by excising the infected eye and fixing it in bichloride whereby the epithelial nodules were emphasized Toomy and Gammel review the literature critically and report their own experience with the Paul test which was positive in 46 per cent of cases

9 McKINNON Neil and DE FRIES Robert O The reaction in the skin of the normal rabbit following intradermal injection of material from small pox lesions the specificity of this reaction and its application as a diagnostic test Am J Hyg 8:93 1928

Although it had been shown long before that the rabbit was susceptible to vaccine virus the effect of smallpox virus had not been clearly demonstrated according to McKinnon and De Fries These authors were able to produce in normal rabbits a definite papular lesion by injection of material from smallpox cases The specificity of the reaction was shown by the failure of subsequent vaccination with vaccine virus to "take" Material from chicken pox failed to elicit a reaction in rabbits The same writers ("The laboratory diagnosis of small pox virus utilizing the rabbit" *ibid* p 107) proposed as a diagnostic test for smallpox the injection of suspected material into normal and vaccine immunized rabbits The specific lesion should of course develop in the former

10 HEDRICH A W Changes in the incidence and fatality of small pox in recent decades Pub Health Rep 51 363 1936

There is a popular idea that vaccination has largely eliminated smallpox in the United States as well as elsewhere and that if the disease occurs it is usually mild Nothing could be further from the truth There were nearly 400 000 cases in the United States from 1921 to 1930 and the death rate per 100 cases varied up to 42 3 in British India All these matters are discussed in detail in Hedrich s paper including the view that there are distinct mild and severe strains of smallpox virus which account for these variations It is thought that the mild virus is responsible for such relatively innocuous entities as "alastrim"

11 LAZARUS A S EDDIE B and MEYER K F Propagation of variola in the developing egg Proc Soc Exper Biol & Med 36 7 1937

Using material from a smallpox vesicle the writers inoculated the chorio allantoic membrane of the developing chick and were able to carry the virus through forty five passages Discrete yellowish white lesions were seen on the membrane several days after inoculation and impression smears showed typical Paschen bodies (Ref 6) with Morosow s stain (M A Morosow "Die Farbung der Paschenschen Korperchen durch Versilberung" Centralbl f Bakt 100 385 1926) The presence of virus was also confirmed by the complement fixation test (James Craigie and F O Wishart "The complement fixation reaction in variola" Canad J Pub Health 27 371 1936) Others also were soon successful in growing the virus of smallpox in chick embryos C John

Buddingh (Infection of the chorio allantois of the chick embryo as a diagnostic test for variola" Am J Hyg 28 130 1938) also injected chick embyros with material from smallpox pustules and produced a pock in which Paschen granules were found and also Guarnieri bodies A W Downie and K K Dumbell ("The isolation and cultivation of variola virus on the chorio allantois of chick embryos" J Path & Bact, 59 189 1947) also described inclusion bodies in chick embryo variola

12 PARKER Robert F Variola and vaccinia *in* Diagnostic procedures for virus and Rickettsial diseases p 83 New York American Public Health Association 1948

The early diagnosis of smallpox becomes especially necessary before an epidemic is under way *The disease may be confused with chicken pox influenza* or other infections Laboratory diagnosis is therefore very important Parker summarizes the modern status of the subject in this article We have alluded to various tests in the course of this bibliography (Refs 7 8 9 10)

13 DOWNIE A W McCARTHY K M and MACDONALD Alexander Viremia in small pox Lancet 2 513 1950

Downie and Dumbell (Ref 11) had isolated virus from the blood of a case of hemorrhagic smallpox on the fifth day Downie and his colleagues however successfully inoculated chick embryos with blood drawn in the very early stages of the disease before the rash was distinctive in four of seven patients F O MacCallum C A McPherson and D F Johnstone ("Laboratory investigation of small pox patients with particular reference to infectivity in the early stages Lancet 2 514 1950) were able to recover smallpox virus by egg inoculation with blood drawn the day before and on the day of onset of the rash They also recovered the virus from throat swabs taken in the early *stages of the disease The viremia of smallpox evidently occurs early* and is more likely to be demonstrable in very severe cases These writers following others also suggest that the portal of entry of smallpox virus is by way of the respiratory passages Downie ("Infection and immunity in smallpox" Lancet 1 419 1951) further studied the development of smallpox in relation to immunity and antibody formation His concept is as follows The site of entry of the virus is in the upper respiratory tract A minimal lesion occurs and the virus quickly passes to lymphatic glands and by blood stream to internal organs Increase of virus in these organs takes place during the incubation period. At onset of illness there is an overflow of virus into the blood stream and liberation of the products of cell breakdown The skin and other tissues are infected with virus at this time and in most cases the immune response with the formation of antibody follows a few days later The speed and extent of the antibody formation determines the extent of the rash and the severity of the disease Antibody persists at a high level for some years after smallpox Thus the eruption at its height is really an antigen antibody reaction

Section 26

VACCINIA

Animal vaccine	Ref 9
Cowpox	Refs 1 2 3 24
Cultivation of virus	Ref 15
Elementary bodies	Refs 20 22 23 25 26
General	Ref 1
Growth of virus in chick embryo	Ref 21
History	Refs 8 12
Immunity	Refs 10 14 20 22
Jennerian vaccination	Refs 1 2 3 4 5 6 7
Lymph preparation	Refs 9 16
Pathology	Ref 13
Purification of virus	Ref 17
Retrovaccination	Ref 9
Untoward reactions	Refs 18 19
Vaccinial encephalitis	Ref 18

Section 26

VACCINIA

IT HAS been difficult to decide whether one should combine the bibliographies of smallpox and vaccination or keep them separate The two diseases are so closely related caused as they are by viruses in many ways identical that there is necessarily much overlapping in the literature Although it finally seemed better to have separate bibliographies the two should obviously be read and studied together Thus the general and bibliographical references which we have given for smallpox refer also to the literature on vaccination Cross references between the two are designated S" and "V" respectively

1 JENNER Edward An inquiry into the cause and effects of the variolae vaccinae a disease discovered in some of the western counties of England particularly Gloucestershire and known by the name of the cow pox London Printed for the author by Sampson Low 1798

Thus is the famous work in which Jenner claimed that inoculation with material from cowpox conferred protection against smallpox With the lapse of time Jenner's contentions have been amply confirmed, as everyone knows and he stands out in history as a great man and a benefactor of humanity But this was not always so and at the time both the doctrines and the findings of Jenner were by no means universally accepted It has been alleged that Jenner was not a critical scientist indeed some claim that he was little more than a quack First of all it is said that the idea of cowpox conferring protection against smallpox was not novel with Jenner but was currently popular among dairy folk and cow leeches at the time It is stated that one B Jesty a farmer of Downshay in the Isle of Purbeck in 1774 inoculated his wife and two sons from his cows and that subsequently they resisted the most rigorous trials to confer smallpox upon them It is claimed that cowpox is not really a "pock" disease that mere resemblance of names—cowpox smallpox—somewhat irrationally stimulated Jenner to develop his doctrine and that aside from the name there was no more resemblance between the two disorders than there is between a horse chestnut and a chestnut horse In 1796 or 1797 Jenner drew up a report of one case that of James Phipps whom he inoculated with material from a cowpox vesicle on the hand of the dairymaid Sarah Nelmes The vaccination took and inoculation with variolous matter later failed to produce disease This paper was sent informally to the Royal Society who evidently did not feel that the evidence was conclusive and it was not until 1798 that Jenner himself published the famous "Inquiry" All these matters are discussed in detail in Charles Creighton's book, *Jenner and Vaccination* (London Swan Sonnenschein & Co 1889) which takes a bitterly antagonistic attitude toward Jenner as well as in Edgar M Crookshank's *History and Pathology of Vaccination* (London H K Lewis 1889) which preserves a somewhat more temperate attitude Edward J Edwardes *A Concise History of Small Pox and Vaccination in Europe* (London H K Lewis 1902) on the

other hand, deals with the same transactions but in a spirit highly favorable to Jenner

Now as to the "Inquiry" itself After an introductory paragraph Jenner turns immediately to discussion of a disease of horses called "the grease" "It is an inflammation and swelling in the heel from which issues matter possessing properties of a very peculiar kind which seems capable of generating a disease in the Human Body (after it has undergone the modification which I shall presently speak of) which bears so strong a resemblance to the Small Pox, that I think it highly probable it may be the source of that disease" Jenner goes on to claim in brief that milkers may contaminate cows with material from "the grease" which produces cowpox, which in turn may be transmitted to the milkmaids "Thus the disease makes its progress from the Horse to the nipple of the Cow and from the Cow to the Human Subject but what renders the Cow Pox virus so extremely singular is that the person who has been thus affected is forever after secure from the infection of the Small Pox neither exposure to the variolous effluvia nor the insertion of the matter into the skin producing this distemper" This does seem a somewhat rash claim on Jenner's part since it was common knowledge at the time that those who were "Cowpoxed" might later have smallpox even today we know that a successful vaccination does not confer permanent protection but must be repeated every few years Jenner continues "In support of so extraordinary a fact I shall lay before my Reader a great number of instances" At this point Jenner states in a footnote that one must beware of confusion arising from another variety of "pustulous sores" which "frequently appear spontaneously on the nipples of Cows and instances have occurred though very rarely of the hands [of milkers] being affected with sores in consequence and even of their feeling an indisposition from absorption" This disease is however quite different, he claims from that caused by infection from horse "grease" and infection with material from this sort of spurious cowpox confers no immunity "But this disease is not to be considered as similar in any respect to that of which I am treating as it is incapable of producing any specific effect on the human Constitution However it is of the greatest consequence to point it out here lest the want of discrimination should occasion an idea of security from the infection of the Small Pox which might prove delusive" There follow twenty three case reports some of people who gave a history of having had the cowpox and whom Jenner found resistant to inoculation with variolous material, and some of people whom Jenner inoculated with "Cow Pox" material produced disease and then found them resistant Case IX opens with the following interesting statement "Although the Cow Pox shields the constitution from the Small Pox yet it appears that the human body is again and again susceptible to the infectious matter of the Cow Pox" William Smith had contracted the disease in 1780 "One of the horses belonging to the farm had sore heels and it fell to his lot to attend him By these means the infection was carried to the cows and from the cows it was communicated to Smith

In the year 1791 the Cow Pox broke out at another farm where he then lived as a servant and he became affected with it a second time and in the year 1794 he was so unfortunate as to catch it again It must be admitted that case histories of this sort are of little scientific value The role of the horse

"grease is mentioned in a number of patients as in Case XV "Although in the two former instances the system seemed to be secured or nearly so from variolous infection by the absorption of matter from sores produced by the diseased heels of horses yet the following case decisively proves that this can not be entirely relied upon until a disease has been generated by morbid matter of the horse on the nipple of the cow and passed through that medium to the human subject Mr Abraham Riddiford in consequence of dressing a mare that had sore feet was affected with lesions regarded as those of Cow Pox but being exposed to small pox twenty years later contracted the disease" It was on evidence of this sort that Jenner claimed that the original disease of the horse must be catalyzed" in the cow before true cowpox could be produced Case XVI *is the famous one of Sarah Nelmes from whose pustulous* sore Jenner inoculated the eight year-old boy (Case XVII) by means of "two superficial incisions barely penetrating the cutis each about half an inch long" On the seventh day he developed malaise and dulness and maturation of the incisions" He was later twice inoculated with variolous matter without developing smallpox Jenner then described the cases of two farm hands Haynes and Virgoe who, in spite of the fact that they had gone through the smallpox from inoculation developed from a mare with sore heels sores in their hands followed by inflamed lymphatic glands in the arm and axillae" etc Haynes was daily employed as one of the milkers at the farm and the disease began to shew itself among the cows about ten days after he first assisted in washing the mare s heels Their nipples became sore in the usual way" Jenner s later cases were inoculated with cowpox and and then did not take smallpox inoculation

The last half of the "Inquiry consists of a rather rambling general discourse on the subject "May it not then be reasonably conjectured that the source of the Small pox is morbid matter of a peculiar kind generated by a disease in the horse and that accidental circumstances may have again and again arisen still working new changes upon it until it has acquired the contagious and malignant form under which we now commonly see it making its devastations amongst us?

It seems to us very difficult to evaluate all this The great fact stands out that Jenner s main thesis has turned out to be correct but was this a lucky guess as some have claimed or does his published evidence really justify his conclusions? Certainly his position with reference to horse "grease" and true and spurious cowpox was weak

That there followed a long period during which the value of vaccination was variously judged is quite intelligible First of all despite Jenner it was common knowledge that some of those who had had the cowpox *did* later acquire *smallpox Then when we consider that the procedure source of virus collection* and preservation of it and mode of inoculation were absolutely unstandardized and haphazard, that supposed cowpox virus was probably often contaminated with smallpox virus and that the lesions produced by vaccination were almost always infected with secondary invaders there is small wonder that many were confused

2 PEARSON George An inquiry concerning the history of the cow pox principally with a view to supersede and extinguish the small pox London J Johnson 1798

Pearson published in support of Jenner shortly after the "Inquiry" appeared He collected evidence on all sides from both physicians and laymen as to immunity to smallpox in those who were cowpoxed. He lists Jenner s claims in a series of propositions and adduces evidence in support of all except the one which states that a person may have cowpox over and over again and yet be immune to smallpox "They [the professional men] are not averse from admitting the evidence that the Cow Pox may affect the same constitution repeatedly or even that a person having had this disease is insusceptible of the Small Pox but that the constitution having suffered the Cow Pox should still be susceptible of this disease and not susceptible of the Small Pox is an assertion with regard to which they demur to acquiesce"

3 WOODVILLE William Reports of a series of inoculations for the variolae vaccinae or cow pox with remarks and observations on this disease considered as a substitute for the small pox London James Phillips & Son [1799]

Woodville who was physician to the Smallpox Hospital in London and who had a vast experience in smallpox inoculation was naturally interested in Jenner s work This report begins with experiments in which he inoculated the nipples of cows "with matter of the grease of horses" without any effect Cow pox later broke out in a dairy and was clinically identified by a panel of expert physicians whom Woodville took there to see the lesions Sarah Rice a milk maid was also affected with a vesicle on her hand similar to those described by Jenner Woodville inoculated two hundred people with cowpox lymph obtained fortunately early in the disease Many of these inoculations were from person to person There are detailed notes on the cases and a long table giving the patients names and the number of pustules produced a good many had a large number of pustules several as many as six to seven hundred There may have been some confusion with smallpox but at any rate Woodville did the first major operation of vaccinating a large number of people and he supplied lymph to many physicians including Jenner

4 JENNER Edward Further observations on the variolae vaccinae or cow pox. London Printed for the author by Sampson Low 1799

In order to explain contradictions which were reported on many sides Jenner here tries to define the genuine cowpox and the specifications for a reliable virus "I shall proceed to enumerate the sources or what appear to me as such of a spurious Cow Pox 1st That arising from pustules on the nipples or udder of the cow which pustules contain no specific virus 2ndly From matter (although originally possessing the specific virus) which has suffered a decomposition either from putrefaction or from any other cause less obvious to the senses 3dly From matter taken from an ulcer in an advanced stage which ulcer arose from a true Cow Pock 4thly From matter produced on the human skin from contact with some peculiar morbid matter generated by a horse"

More and more difficulties and contradictions were being encountered but, through it all Jenner remained steadfast to his fundamental thesis

In still another communication Jenner (*A Continuation of Facts and Observations Relative to the Variolae Vaccinae or Cow Pox* [London Printed for the author by D N Shury 1801]) replied to Dr Woodville (Ref 3) who produced multiple pustules in so many of his vaccinated patients Jenner believed probably correctly that smallpox virus had somehow entered Woodvilles vaccine and that the cases with many pustules were instances of small pox All this shows how confused the entire situation was at the time

5 WATERHOUSE Benjamin A prospect of exterminating the small pox being the history of the variolae vaccinae or kine pox commonly called the cow pox as it has appeared in England with an account of a series of inoculations performed for the kine pox in Massachusetts Cambridge Cambridge Press William Hilliard 1800 Also Part II Cambridge 1802

Waterhouse deserves credit for introducing vaccination into the United States He became interested in vaccination in 1799 when he read Jenners "Inquiry" In June 1800 he received some "matter" from England and promptly vaccinated his children "I commenced the experiment on July 8th, 1800 on my own children four of whom with three of my domestics passed regularly through the distemper and that they soon after went into the licensed small pox hospital in this neighborhood and all seven of them were inoculated by Dr Aspinwall with the matter of small pox without the least trace of infection" (Part II p 5) The whole story of Dr Waterhouse is told by Robert H Halsey (*How the President Thomas Jefferson and Dr Benjamin Waterhouse Established Vaccination as a Public Health Procedure* [New York The Author 1936]) Waterhouse received requests from the southern states for information about vaccination These led him into correspondence with Thomas Jefferson "Young and inexperienced practitioners are most forward in their business yet such can neither excite attention nor inspire confidence whereas if it came from Mr Jefferson it would make like a body falling from a great height a deep impression" (Part II p 25) The President immediately put the matter into the hands of a long-established, judicious and successful physician but various lots of vaccine failed to take perhaps because of the very hot weather But on August 6 1801 takes were obtained at Monticello on some of the Presidents family Part II deals systematically with the whole subject of "kine pox" and vaccination

6 JENNER Edward The origin of the vaccine inoculation London Printed by D N Shury 1801

In this brief communication Jenner tells how he became interested in the subject twenty five years previously He outlines his work and the arguments in its favor "A hundred thousand persons upon the smallest computation have been inoculated in these realms The number who have partaken of its benefits throughout Europe and other parts of the globe are incalculable and it now becomes too manifest to admit of controversy that the annihilation of the Small Pox the most dreadful scourge of the human species must be the final result of this practice

7 BROWN Thomas An inquiry into the antivariolous power of vaccination in which from the state of the phenomena and the occurrence of a great variety of cases the most serious doubts are suggested of the efficacy of the whole practice and its powers at best proved to be only temporary From which also will appear the necessity of and proper period for again submitting to inoculation with variolous virus Edinburgh Archibald Constable & Co 1809

For years after the publication of the "Inquiry" (Ref 1) the medical and indeed the civilian world was in a ferment of argument about the safety and value of Jennerian vaccination There were the camps of the vaccinationists and the antivaccinationists Innumerable books and pamphlets appeared attacking or in defense of the practice Some of the antivaccinationist literature was bitter unreasonable and scurrilous and was motivated by envy or hate But there were other writers who in cool appraisal of the whole situation noted weak spots in Jenner s arguments and in the results of practice even though the pendulum swung wildly in favor of vaccination and the procedure was officially approved by the Royal College

Brown gives a temperate analysis of the vaccination problem and astutely notes the obvious flaws in Jenner s argument "The vaccine practice was introduced and recommended to the public by its author as a perfect antidote and security against the smallpox without any exception or reserve and if properly patronized capable of banishing variola from the catalogue of human misery"

All who have wrote upon the subject have acquiesced with the grand results of its author and have practised and patronized it with a zeal hitherto unexampled" (p 2) He then complains that anyone who has in any sense criticized vaccination is regarded as a backward looker and obstructionist "It has been also asserted that it had to encounter the opposition of designing and ignorant men It must be confessed that at the commencement of the practice an opposition arose from a few individuals of the profession but so far from thinking it was inimical to the new practice I am convinced that it contributed not a little to increase its reputation and to extend its influence" (p 4) He continues with a critical analysis of the experiences of Jenner and others

The most important part of the book is however a series of case reports of people who had undergone vaccination meeting all the criteria of a successful procedure who later had smallpox He maintains the thesis which of course is correct that vaccination does not confer permanent protection but that revaccination is always necessary after an appropriate period To these material considerations we add that the Royal College of Physicians and the Royal Jennerian Society in London admit that cases of small pox have occurred where sufficient proof has existed of the most perfect vaccination" (p 276) "To these statements of such respectable public bodies we have to add those cases given by various others "such an accumulation of proof is afforded, as not only to abolish all parallel betwixt the two diseases in this respect but to point out in the most striking manner the *temporary* and *feeble* protection afforded by vaccination against variolous contagion" (p 277) Interestingly enough Brown does not advise revaccination at appropriate intervals but urges the abandonment of vaccination altogether and a return to variolation Brown was correct in his claim that vaccination did not confer permanent protection

but his conclusion was wrong and fortunately the pendulum continued to swing strongly to vaccination all over the world It is easy to see however how difficult it must have been for honest critical observers to evaluate the whole situation at the time

Brown s book is of the greatest interest and must be read to grasp its full implications

8 MOORE James The history and practice of vaccination London Printed for J Callow 1817

Moore who was director of the National Vaccine Establishment devotes the first few chapters of his book to telling the story of Jenner s work and of the early supporters and detractors of vaccination The discovery of a mode of preventing the Small Pox is one of those splendid events which reflect lustre on the English nation and it must be interesting to learn whether this was stumbled upon by chance, or unfolded by ingenuity" (p 1) a question perhaps not entirely settled today Chapter vi is devoted to "The reception of the vaccine with the public in England" Moore points out that in one year vaccination was diffused throughout Europe and in less than three reached India and China "It is remarkable that the opposition to Vaccination was much more violent in England where it was discovered than in other countries" (p 115) He even suggests that some doctors may have been hostile to the elimination of a disease which contributed heavily to their practice However "Vaccination in the year 1799 acquired the powerful support of the Commander in Chief" the Duke of York, who as soon as the Army Medical Board and other competent judges had given full assurances and complete proofs that this was the case a general order was issued to vaccinate every soldier who had not had the Small Pox *By this measure the malady was at once extinguished in* the army and many a gallant soldier preserved After a short time the Lords of the Admiralty imitated this excellent example" (p 119) The difficulty in finding a ready supply of lymph was for a long time a considerable obstacle to the diffusion of the vaccine" (p 120) Apparently the lymph was gained mainly from vaccinated patients and was passed around informally by anyone who had a supply Meanwhile feelings about vaccination became emotional if not hysterical in July 1800 a declaration was framed in favor of vaccination signed by laymen and physicians and to be followed by other such documents "Some country ladies even ventured to make use of the lancet and resolutely vaccinated every child whose parents they could prevail on by insinuation or entreaties to confide in their skill (p 123)

On March 17 1802 Jenner presented a petition to the House of Commons for reimbursement of financial outlay and loss in connection with vaccination "The business was then referred to Committee of which Admiral Berkeley was appointed chairman The committee held hearings and gathered elaborate testimony from many physicians and then drew up a report "expressed in as favourable terms towards Dr Jenner as the caution and formality of parliamentary language would admit" (p 159) The interesting debates upon the measure are quoted in detail by Moore "The House then divided upon the original motion for granting £10 000 which was carried by a small majority of three" (p 174)

The action of Parliament "enabled the Vaccine to assume a more lofty de meanor"—in other words it gave both the vaccine and Jenner a "boost" In 1806 Lord Henry Petty again brought the matter before the House of Commons He quoted favorable statistics on the decline of smallpox (in Vienna for example before vaccination about 835 died each year of smallpox whereas in 1804 there were only 2 deaths from this cause) and he moved that the king direct the Royal College of Physicians to inquire into the state of vaccine inoculation in the United Kingdom The college made an elaborate investigation and reported favorably Among 164 381 persons vaccinated there were only 66 in whom eruptions of the skin followed Other important colleges made similar reports The question of a further reward for Dr Jenner was again taken up by the House and after a lively debate on July 29 1807 the House divided "upon the question that twenty thousand pounds should be granted to Dr Jenner sixty votes were in favour of this sum and forty seven against it" (p 209)

In chapter x Moore discussed vaccine institutions It had early been per ceived that "the extension of the new practice was much retarded by the want of a constant and convenient supply of Vaccine lymph" Jenner resolved to establish a Vaccine Society and to place the medical department under the direction of the most eminent professional gentlemen in London" (p 210) "Accordingly in 1803 proposals to that effect were printed and circulated The plan met with the most distinguished approbation for the King Queen and every British Prince and Princess accepted the title of Patrons and Patronesses and multitudes of the nobility and gentry became members of an Institution which by unanimous consent was denominated the Royal Jennerian Society" (p 211) But the society had its difficulties with the distribution of lymph and with vaccinating and in 1808 Parliament created the National Vaccine Establishment Seven stations were set up in London for vaccinating all who should apply and for collecting and distributing vaccine lymph to those who wished it "In 1816 7771 persons were vaccinated by this Establishment alone and 44 376 charges of lymph were distributed to the public" (p 223)

The remainder of the book tells how vaccination was introduced within a few years all over Europe and indeed all over the world Lymph was shipped apparently dried and was successfully used even as far away as Turkey and the West Indies

The final chapter is on the "Practice of vaccination" "The instructions of the National Vaccine Establishment of London were founded upon the experi ence of many [pp 274 ff] and improved by successive observations The first consideration is the time to be chosen for vaccination The exquisite irrita bility of a new born infant and the uncertainty of its organization being per fect are sufficient motives for usually deferring the operation until three weeks after birth But when the Small Pox infection is at hand this superlative danger overwhelms all other considerations and every human being susceptible of the poison without exception should instantly be vaccinated Lymph for vaccination should only be taken from a vesicle perfectly regular while the vesicle is uninjured and proceeds in its due course the lymph certainly pre serves its specific quality but should it be irritated and any undue inflammation excited rendering the secretion purulent this is to be considered as vitiated and unfit for use If surgeons could find a constant succession of subjects

pure lymph in its early and most active state should always be employed and Vaccination performed by transferring the transparent lymph directly from arm to arm a little is to be taken up on the point of a lancet and introduced slantingly into the skin of the arm under the cuticle until it touches the cutis When pointed quills or bits of ivory are well and repeatedly moistened with lymph they preserve the virtues of the Vaccine for a long time [1]

There are several other methods in use for preserving vaccine lymph A drop is sometimes inclosed between two bits of square glass or it may be deposited in a small cavity hollowed out of the centre of a piece of ground glass and covered accurately with a flat piece of the same size Lymph desiccated on glass is brought to a proper state for use by mixing it up with a particle of cold water by the point of a lancet' A most important observation was also made by James Bryce F R S (*Practical Observations on the Inoculation of Cow Pox* [Edinburgh 1802]) which anticipated Von Pirquet (Ref 14) by one hundred years "This gentleman indeed tried the effect of revaccination during every period of the progress of a vaccine vesicle He noticed that when the first operation succeeded, the inflammation excited by the second was accelerated, and as soon as the primary vesicle acquired the areola the second however small it might be also acquired a proportional areola and both dessicated together" (p 287)

Many more details are given indeed we have only touched a few high spots of this invaluable contemporary account of the state of vaccination

Debate about the merits and safety of vaccination has continued however and much has been written even in modern times in defense of the procedure Ernest Hart for example who was chairman of the National Health Society (England) felt it necessary to write a pamphlet, *The Truth about Vaccination An Examination and Refutation of the Assertions of the Anti Vaccinators* (London Smith Elder & Co 1880) and similar material continues to be published today

9 CEELY Robert Observations on the variolae vaccinae Tr Provincial M & Surg A 8:287 1840

Ceely asks a question which had been much in the air practically ever since vaccination was extensively practiced "Is vaccine lymph in passing through many individuals with all due care and selection susceptible in process of time of actual degeneration or essential diminution of intensity?" The writer of course refers to the usual practice of vaccination by means of lymph derived from people previously vaccinated Ceely reviews the question quoting authorities who judged the question in various ways The National Vaccine Establishment in a report ordered by the House of Commons to be printed April 11 1838 ("Vaccine Institution Copy of the last report from the National Vaccine Establishment to Her Majesty s Principal Secretary of State for the Home Department" London M Gaz 22 349 1838) declared "No it has not worn out its protecting property" M J B Bousquet (*Traité de la vaccine* [Paris J B Baillière 1833] p 217) also felt that there had been no diminution of intensity in comparing an old lymph transferred since 1800 with new vaccines

1 As late as 1900 the writer recalls being vaccinated by means of an ivory "point with vaccine dried on it, which Dr B— produced from his waistcoat pocket.

George Gregory ("Report laid before the General Court of Governors of the Small Pox and Vaccination Hospital 1st of February 1838" London M Gaz 21:860 1838) on the other hand stated "The lymph in use at this hospital had been preserved in uninterrupted descent for a very long period of time but for three or four years past I had noticed that its intensity was diminished " Many authorities could be collected on both sides but at any rate it was doubt about much of the current vaccine which led to efforts to restore its potency by again passing it back to the cow Ceely himself attempted to do so without good success but retrovaccination so called, soon became popular and successful The subject is reviewed in Dr Edward Ballard s excellent book *Vaccination* (London Longmans Green & Co 1868) According to Ballard Negri in Italy had for a long time been successful in transferring the vaccine from calf to calf and using calf lymph for human vaccination In 1865–66 there were great discussions in France as to the procedure but M Depaul ("Discussion sur la vaccination animale" Bull Acad de méd Paris 32:1024 1867) seems to have been most instrumental in introducing vaccination from calf lymph Ballard describes the method of vaccinating the calves as he saw it in Paris "The operator then proceeds to shave with a dry razor the right side of the abdomen commencing from the udder and extending over a space of about ten inches long by six or eight broad The calf which is the vaccinifer from which the virus is to be taken is also securely fastened down and the vaccine matter is obtained from the pock by forcible compression of its base with a pair of spring forceps The animal on the table is vaccinated upon the shaven surface by puncture in sixty or seventy places Pocks which finally attain the size of large human vaccine pocks speedily begin to rise and are used for the vaccination of children from the fourth to the sixth day" (p 254)

Calf virus seems to have been imported to the United States by Dr Henry A Martin in 1870 ("Animal vaccination" Boston M & S J 83 254 1870) Martin sent an agent to Paris who received from Dr Depaul virus from calves through which the virus had been transmitted since originally started from a cowpox strain discovered at Beaugency[2] by Depaul in 1866 The virus arrived in this country safely and was successfully propagated and used for vaccination by Dr Martin In a few days I shall have such arrangements completed as will enable me to invite all who may feel an interest in animal vaccination to see the disease in the heifer to bring patients to be vaccinated therefrom and to obtain if it is desired their supplies directly from the source" The whole subject was thoroughly discussed a few years later by Martin in a long article "Report on animal vaccination" Tr Am M A 28:187 1877

Several points remain to be made clear As to definitions in the contemporary literature "retrovaccination refers to virus from a vaccinated human being which is reimplanted in the heifer animal vaccine on the other hand "is the product of natural horse-pox or cow pox which has been cultivated on heifers and has never quitted that soil" It is stated by nearly every contemporary writer although we have been entirely unable to find the original reports that

[2] The story of the discovery of this famous case of cowpox is told by M Depaul ("Cowpox spontané" Bull Acad. de méd 31:590 1866) "It was on a heifer thirty months old, belonging to M Drouin Mercier farmer at Beaugency that the cow pox arose spontaneously It was from her that the virus was passed from calf to calf for years to produce Depaul s stock of vaccine

animal vaccination was extensively practiced in Italy from 1810 on by Galliati and later by his pupil Negri It is stated that in 1865 Dr Larroux of Paris made a trip to Naples to view Negri s work and brought home with him a heifer which had been vaccinated from which vaccinia was passed to other heifers from which physicians were supplied with lymph (Ballard *op cit* p 247 E Warlemont, *A Manual of Animal Vaccination* [Philadelphia John Wyeth & Bros 1886] p 77 Martin "Report on animal vaccination" p 200)

The fact that a decline in the immunizing power of vaccine results from lengthy passage through the same vaccinifer has been confirmed in modern times as for example, by Blaxall (Ref 16) and by J Cunningham ("A note on the degeneration of vaccine lymph on passage through the same vaccinifer Indian J M Research **15** 373 1927)

10 RAYNAUD Maurice Étude expérimentale sur le rôle du sang dans la transmission de l immunité vaccinale, Compt rend Acad d sc **84** 453 1877

Raynaud performed an interesting and early experiment on the immunity of vaccination A calf which had been vaccinated 6 days previously and was in full vaccinial eruption" was bled for 200 cc The blood was immediately transfused into the jugular vein of a three month-old calf There was no reaction After 15 days sixty inoculations of fresh vaccine were made into the mammary region all failed to take and did not yield a single pustule Another calf vaccinated at the same time with the same vaccine broke out 4 days later with a "magnificent vaccinial eruption " Raynaud concluded that under the conditions of his experiment the blood contained a "principle capable of transmitting immunity

Another early immunological experiment was that of George M Sternberg ("Practical results of bacteriological researches" Tr A Am Physicians **7** 68 1892) He found that vaccine virus mixed with serum from a vaccinated (immune) calf failed to produce a pustule when used to vaccinate a second calf whereas virus mixed with serum from an untreated calf produced a good "take"

11 KLEBS E Der Micrococcus der Variola und Vaccine Arch f exper Path u Pharmakol **10** 222 1879

It was inevitable that during the early days of the bacteriological era ordinary bacteria should be blamed as the cause of smallpox Klebs the great bacteriologist fell into this error and thought that he found a coccus regularly in smallpox and vaccine lymph "The essential result of our investigations may be summarized by saying that the organisms of Vaccinia and Variola occur exclusively in the form of micrococci that they assume no other form in any stage of development than that of tiny spherules

12 EDWARDES Edward J A concise history of smallpox and vaccination in Europe London H K Lewis 1902

There are innumerable statistics on vaccination and smallpox This little book contains an excellent and comprehensive summary largely in tabular form of the dates when vaccination was introduced into various countries when it was made obligatory and the number of cases of smallpox in relation to the vaccinated Rules in force in Britain have been described by Blaxall (Ref 16) and

in the United States by William Fowler ("Principal provisions of smallpox vaccination laws and regulations in the United States" Pub Health Rep 56:1 1941)

In this connection it is of interest to read the *Memorial of Board of Commissioners of Health of the City of New York on the Subject of Compulsory Vaccination with a View To Exterminate the Small Pox* (New York Wm H Trafton & Co 1862) drawn up by Dr Lewis A Sayre resident physician strongly favoring compulsory vaccination

13 TYZZER E E The etiology and pathology of vaccinia J M Research 11 180 1904

Tyzzer made elaborate anatomical studies of vaccinia lesions including those of the corneas of rabbits and of calves which had been inoculated with vaccine virus There are beautiful plates of the lesions Tyzzer however like Councilman (Ref S5) went wrong in concluding that the inclusion bodies were a highly organized parasite

14 PIRQUET C von Die fruhzeitige Reaction bei der Schutzpocken impfung, Wien klin Wchnschr 19 855 1906

Although Bryce in 1802 (Ref 8) had described accelerated vaccine reactions little further interest was taken in the subject until Von Pirquet the great Viennese pediatrician conducted his systematic studies Von Pirquet approached vaccination from the standpoint of allergy He first carefully noted the time element in the various stages of a vaccination lesion and then studied in comparison, early and late revaccinations Theoretically one would expect a second vaccination to proceed more slowly than the first in an immune or partially immune body Actually the reaction is accelerated "Vaccination produces no absolute immunity but it alters the reactivity of the body in such a way that it reacts earlier and brings the repeated infection to its conclusion in shorter time" Working along these lines Von Pirquet made fundamental contributions to the theory of allergy and immunity Later he ("Ist die vakzinale Fruhreaction specifisch? Wien klin Wchnschr 19:1407 1906) answered Kraus s criticism that the accelerated reaction was not specific He reported careful experiments from which he concluded "1 The vaccinal early reaction is a specific reaction between the cowpox lymph and the organism which has been rendered immune (or allergic) to it 2 The early reaction is quantitatively dependent on the amount of the virus which is introduced and is distinct from a first vaccination in which the size of the reaction is independent of the amount of infectious material"

Von Pirquet amplified these fundamental studies in a book *Klinische Studien uber Vaccination und vaccinale Allergie* (Leipzig and Vienna Franz Deuticke 1907)

15 NOGUCHI Hideyo Pure cultivation in vivo of vaccine virus free from bacteria J Exper Med 22 539 1915

Although it had been shown (for literature see Ref S5) that the virus of small pox may localize in various organs less was known about the circumstances in connection with vaccine virus Noguchi succeeded in adapting a strain of vaccine virus to testicular growth by passage through testes of rabbits and bulls

The multiplication of the virus within the testicle is maximum on the fourth or fifth day after inoculation the quantity of virus remains about stationary until the eighth day when diminution begins At the expiration of five weeks no more virus could be detected " This pure virus produces typical vaccine "takes" in human beings Further characteristics of this virus are described in another paper by Noguchi ("Further studies on the properties of pure vaccine virus cultivated in vivo J Exper Med 27 425 1918) T P Hughes R F Parker and T M Rivers (Immunological and chemical investigations of vaccine virus " J Exper Med 62 349 1935) were able to obtain appreciable amounts of elementary bodies of vaccinia in a relatively pure state This material contained components similar to those found in bacteria and other substances of protoplasmic origin

A Marie (De l inoculation intracérébrale de la vaccine " Compt rend Soc de biol 83 476 1920) produced an encephalitis by introcerebral inoculation of rabbits with vaccine virus He was able to transmit the disease in series although C Levaditi P Harvieu and S Nicolau ("Affinités neurotropes du virus de la vaccine Compt rend Soc de biol 85 345 1921) had less complete success

At any rate the principle is brought out that vaccine virus may become adapted so that it has a special affinity for various tissues (for further discussion see Van Rooyen and Rhodes *loc cit*)

16 BLAXALL F R Some notes in connexion with the preparation of vaccine lymph at the Government Lymph Establishment Proc Roy Soc Med 15 1 1921 (Sec of Epidemiology and State Medicine)

Numerous accounts have been given through the years of the technique of preparing vaccine lymph An authoritative and detailed description is given by Blaxall including the details of selection of animals housing inoculation collection of virus, etc Blaxall points out that vaccine may be derived from smallpox direct from cowpox or from retrovaccination with lymph from the human arm He recommends passage of lymph through rabbits from time to time in order to "renew the stock " i e to preserve potency The subject was dealt with at length by a committee of the League of Nations in 1928 (*Report of Commission on Smallpox and Vaccination* [C H 739] [Geneva]) A good summary of the practical aspects of vaccination is given in Van Rooyen and Rhodes (*op cit* pp 874 ff)

17 MACCALLUM W G and OPPENHEIMER Ella Hutzler Differential centrifugalization a method for the study of filtrable viruses as applied to vaccinia J A M A 78 410 1922

Although granules (Paschen bodies Ref 57) had been seen for years in vaccine lymph MacCallum and Oppenheimer opened a new era with their attempts to concentrate the effective virus By differential centrifugation of commercial vaccine virus in fluids of varying specific gravity they found that it "floated" in a fluid of specific gravity 1 14 while it "sank" in a fluid of 1 11 "Its own specific gravity is probably about 1 12 or 1 13 " Virus was tested for by inoculating samples of the centrifugates from various levels on the cornea of the rabbit "Examination of a drop of the virulent top layer under the microscope with dark field illumination disclosed myriads of minute granules very

much smaller than streptococci or staphylococci" There seems little doubt that these were the elementary bodies MacCallum promised further work on the subject but none appeared

J C G Ledingham ("The aetiological importance of the elementary bodies in vaccinia and fowl pox" Lancet 2:525 1931) concentrated elementary bodies by a somewhat similar procedure but went a step further in showing that they were specifically agglutinated by immune sera Further development of the subject is well documented in the review by J E Smadel and C L Hoagland (Ref 24)

18 TURNBULL Hubert M and McINTOSH James Encephalo myelitis following vaccination Brit J Exper Path 7:181 1926

J Comby in a general article ("L'Encéphalite aigue chez les enfants" Arch de méd d enf **10**:577 1907) makes the statement that encephalitis may follow vaccination but reports no specific case Turnbull and McIntosh were the first to write systematically on the subject They give careful autopsy reports of seven cases and they conclude that the histological changes were allied to those of poliomyelitis and encephalitis lethargica but showed characteristic differences The virus demonstrated experimentally in brain or cord was a vaccinal virus They also summarize the literature on the specific encephalomyelitis of variola The subject of vaccinal encephalitis is dealt with in detail in the *Report of the Committee on Vaccination Ministry of Health* (London His Majesty's Stationery Office 1928) and in a *Further Report* (1930) and by Van Rooyen and Rhodes (*op cit* pp 393 ff) The latter conclude "It must be realized that postvaccinal encephalitis is only one of a number of diseases which all present a comparable histological appearance demyelinization being the main feature" They did not believe that the mechanism was fully understood

19 GINS H A Impfschaden Zentralbl f d ges Kinderh **24** 145 1930

The question of untoward reactions in connection with vaccination is of interest and importance The idea prevalent in the early days of vaccination that the introduction of animal substance into the human might have a "brutalizing effect" is only of historical interest and the outbreaks of syphilis which were described in connection with vaccination do not of course occur with calf lymph

Generalized vaccinia is an eruption of pustules blood borne which occurs several days after vaccination it is not due to local transfer of virus from the point of inoculation It is a serious complication but fortunately very rare so that from 1920 to 1928 Gins was able to collect only thirteen cases However four were fatal As recently as 1882 however W A Hardaway in his book *Essentials of Vaccination* (Chicago Jansen McClurg & Co 1882) questions the occurrence of general vaccinia (p 56) J Henry Dible and Humphrey H Gleave ("Histological and experimental observations upon generalized vaccinia in man" J Path & Bact 38 29 1934) estimate that this complication occurs about once in a million vaccinations They report a fatal case

Gins systematically describes the various complications of vaccination

20 LEDINGHAM J C G The aetiological importance of the elementary bodies in vaccinia and fowl pox Lancet **2** 525 1931

Ledingham brought forward strong evidence that the Paschen bodies represent the actual virus of vaccinia He found that suspensions of the elementary bodies were specifically agglutinated by convalescent or hyperimmune rabbit sera Normal sera had no effect

21 GOODPASTURE E W WOODRUFF, Alice M, and BUDDINGH G S Vaccinal infection of the chorio-allantoic membrane of the chick embryo Am J Path 8 271 1932

Goodpasture and his associates were the first to grow vaccine virus in the chick embryo Growth with glycerinated (commercial) material was uncertain and better results were obtained if virus from fresh infected rabbit s testis was used The technique of inoculating the eggs is described as well as the appearance of the lesions Guarnieri bodies have been demonstrated for the first time in mesodermal cells (endothelium and fibroblasts) Evidence has been presented that the Guarnieri bodies are composed in part of Paschen corpuscles

22 PARKER R F and RIVERS T M Immunological and chemical investigations of vaccine virus IV Statistical studies of elementary bodies in relation to infection and agglutination J Exper Med 64 438 1936

Although it was generally believed that the relation of the elementary bodies (Ref S7) to infection was a close one these bodies had not been proved to be the actual infectious units Parker and Rivers developed a method for counting the number of elementary bodies in suspensions which were used to infect rabbits and believed that they showed a direct correlation between the number of elementary bodies and the number of infectious units of virus present in a given suspension Parker (Statistical studies of the nature of the infectious unit of vaccine virus J Exper Med 67 725 1938) continued these studies and concluded that the unit of vaccinal virus was particulate and that with certain strains when properly introduced into the skin of the rabbit a single particle was capable of infecting Further work is summarized in Smadel and Hoagland s review (Ref 25)

23 BLAND T O W, and ROBINOW C F The inclusion bodies of vaccinia and their relationship to the elementary bodies studied in cultures of the rabbit s cornea J Path & Bact 48 381 1938

Bland and Robinow s work was directed at the problem of the exact nature of Guarnieri s (Ref S3) inclusion bodies These authors were able to study the development of vaccine virus grown in epithelial cells of the rabbit s cornea in vitro and found that there was a regular sequence of events "We conclude that the inclusion bodies are an obligatory stage in the multiplication of the virus and are colonies of the elementary bodies enveloped in a matrix"

24 TWISTON DAVIES J H JAMES L R and DOWNIE A W Cowpox infections in farm workers Lancet 2 1534 1938

Cowpox has been a somewhat apocryphal disorder and its real relation to human infection and to smallpox has been debated In this study with modern methods the writers describe an outbreak of "spontaneous cowpox in cows and three human cases clearly contracted from the infected cows Interesting immunological observations are reported and the modern literature is reviewed

"The evidence indicates that infection was contracted from lesions on the teats of cattle during the process of milking," just as Jenner had claimed (Ref 1) Some of the patients showed a good antibody response more active against cowpox virus obtained from one of the cases than against a stock strain of virus

To show however how complicated the whole situation is A W Downie and D W Haddock ("A variant of cowpox virus" Lancet 1 1019 1952) were able to isolate on the chorio-allantois of chick embryos a white variant of a cowpox strain which did not produce hemolysis either in the chick embryo or when inoculated into the skin of rabbits The variant bred true

25 SMADEL, J E and HOAGLAND C L Elementary bodies of vaccinia Bact Rev 6 79 1942.

An authoritative review by experts in the field of modern work on the elementary bodies Their identification physical properties morphology chemical nature antigen etc are all discussed

26 NAGLER F P O and RAKE Geoffrey The use of the electron microscope in diagnosis of variola vaccinia and varicella J Bact 55 45 1948

The writers present electron micrographs of the viruses of variola generalized vaccinia and varicella "Virus particles of variola and vaccinia resemble each other very closely in their morphological structure They are undistinguishable from elementary bodies of these viruses derived from the chorio-allantois of the chick embryo" The average size of the elementary bodies of variola or vaccinia was 238 mμ whereas the bodies of varicella were somewhat smaller (210 mμ) All are roughly square or brick shaped. William H Gaylord and Joseph L. Melnick (Intracellular forms of pox viruses as shown by the electron microscope [vaccinia ectromelia molluscum contagiosum]" J Exper Med 98 157 1953) studied with the electron microscope the intracellular development of vaccinia virus and they believe that a process of maturation proceeds through definite stages They think that inclusion bodies are made up of particles in the developmental stage imbedded in a matrix (see Ref 22)

For further details on electron microscopy and size measurement of vaccinia virus see Smadel in Rivers *op cit* pages 429 ff

RABIES

RABIES

THERE are innumerable monographs and books dealing with rabies unfortunately most of these are inaccessible However among the ear lier ones we may mention those of Zinke (Ref 1) and of Krugelstein (Ref 2) and somewhat later that of George Fleming (*Rabies and Hydrophobia* [London Chapman & Hall 1872]) Standard older general articles are those of Bollinger (Die Wuthkrankheit" in H von Ziemssen *Handbuch der speciellen Pathologie und Therapie* (Leipzig F C W Vogel 1874) 3 503 and of A Hogyes *Lyssa* (Vienna Alfred Holder 1897) in both of which there are ex tensive bibliographies These articles have sections on the history of the disease and a comprehensive and readable discussion of this phase of the subject is also to be found in Flemings book (*op cit* pp 7–68) Krugelsteins monograph (Ref 2) contains a most interesting and comprehensive bibliography of the literature before the nineteenth century There is an excellent modern discus sion of rabies with a good bibliography by Harold N Johnson in T M Rivers *Viral and Rickettsial Infections of Man* (2d ed Philadelphia J B Lippincott Co 1952) page 267 and a thorough discussion of the virology of rabies is to be found in C E Van Rooyen and A J Rhodes *Virus Diseases of Man* (New York Thomas Nelson & Sons 1948) pages 792 ff A good introduction to the whole subject is the little book by L T Webster *Rabies* (New York Macmil lan Co 1942)

Finally one should mention the authoritative reviews of P Lépine ("Rage-virus rabique" in C Levaditi and P Lépine *Les Ultravirus des maladies hu maines* [Paris Libraire Maloine 1938] p 395) by J Koch ("Lyssa" in W Kolle and A von Wassermann *Handbuch der pathogenen Mikroorganismen* [3d ed Jena Gustav Fischer 1930] 8, Part I 547) and by R Kraus and F Schweinburg (Ueber die experimentellen Grundlagen der Schutzimpfung gegen Hundswuth Methoden der Schutzimpfung und ihre Resultate" in Kolle and Wassermann *op cit* p 695) The article by Koch has a very extensive bibliography

1 ZINKE Georg Gottfried Neue Ansichten der Hundswuth ihrer Ursachen und Folgen nebst einer sichern Behandlungsart der von toller Thieren gebissenen Menschen Jena Christian Ernst Gabler 1804

Zinke is universally given credit for first transmitting rabies by means of saliva His experiments are crude however and not entirely convincing Experiment No 1 is perhaps the best "I took saliva from a mad dog as soon as he had been killed by means of a little paint brush On the same day I made incisions in the forelegs of a one year-old dachshund and then painted over the wounds as much saliva as the paint brush would hold The dog remained lively and ate and drank until the seventh day on the eighth he ignored his food did not drink was sad and crawled into the corner of his cage and by the tenth day had overt rabies He was therefore killed and buried in the ground"

Zinkes little book contains much more however than these experiments Beginning with an introduction about dogs in general he goes on with a de-

tailed description of canine rabies The second section is on rabies and hydrophobia (*Wasserscheu*) in man After a thorough discussion of contagion he concludes that the disease is transmitted by the bite of a mad dog but denies that the saliva of a non rabid animal can contain the rabies producing substance or that its bite can cause rabies He has no idea however of a *contagium vivum* There follows a description of the disease in man and a speculative discussion of the mechanism of hydrophobia Among various theories is mentioned that which claims an unnatural (*widernaturliche*) increase of nerve action and sensitiveness especially of the organs of deglutition (p 124) He himself regarded hydrophobia as a psychotic phenomenon—a peculiar kind of mania (p 125) As prophylaxis he advised excision of the wound cauterization with a red hot iron or burning out the wound with gunpowder (p 143) He described the special methods of various authorities for treating the wound as for example Schmucker s method" or "Haygarth s method " Schumucker made incisions into the wound rubbed in Spanish fly (Cantharides) and then applied a large plaster of Spanish fly After 12 hours he opened the blisters so as to increase the suppuration etc (p 146) Haygarth on the other hand advised irrigating the wound with warm water for several hours whereas Desault and Sauvages suggested rubbing in quicksilver In Persia according to travelers they made punctures around the wound into which onions were rubbed (p 156) Recently galvanism came into fashion As to internal remedies there are sections on June bugs Spanish fly volatile alkali belladonna baldrian opium taxus quicksilver and copper with references to the advocates of each (p 158)

The book concludes with an admonition that one take care not to be injured by the patient with rabies or to be sprinkled (*bezudelt*) with his saliva and that one be careful not to touch with bare hands objects which have been in his mouth Everything in contact with the patient should be thrown into the fire or buried deep in the ground (p 211)

Thus this little book is a curious mixture of ancient superstition and sound modern ideas

Hugo Alt Graf zu Salm Reifferschied ("Beytrage zu einer Geschichte der Hundswuth " Allg Anzeiger 1 2, 1813) a little later attempted to transmit rabies from a rabid dog which at autopsy showed an inflamed pharynx and lungs congested with blood. Other dogs ate food which had been smeared with saliva obtained during life from the rabid dog or were "vaccinated" ("einimpfung") with liquid or dry saliva one animal, finally ate flesh of the dead rabid dog which was cooked with its food. All developed rabies On the average the disease was manifest by the eighth to tenth day One dog was "cured by cherry wine water belladonna cherries and potassium sulfate [*blausauren Kali*] " Rabid dogs ate well as long as the food was steaming hot as it cooled they ceased to eat We are unable to interpret these observations with finality the interesting point is that the experimenter was convinced that the saliva contained the causal agent and that the disease was communicable

2 KRUGELSTEIN Franz Christian Karl Die Geschichte der Hundswuth und der Wasserscheu und deren Behandlung Gotha In der Hennings schen Buchhandlung 1826

This book of 640 pages on every phase of rabies seems to have been a land mark in its time It opens with a bibliography of some three hundred titles going back to the classical writers and coming up to date Since the same general plan is followed as in Zinke s book (Ref 1) we shall not analyze it in detail Krugelstein thought that there was a rabies producing poison in the sputum but he believed that it originated *de novo* under various conditions Neither he nor Zinke had any idea of a living agent On the other hand he says (p 332) "Rabies or hydrophobia is without doubt a disease of the nervous system If any nerve ending is infected by the saliva poison it sickens locally and sends the poison along until by way of the sympathetic nerves it reaches the coeliac plexus and thence affects the entire nervous system From there it spreads by way of the spinal cord and in the involvement of the centers of mood [*Stimm nerven*] the disease reaches its acme" Thus Krugelstein clearly insisted on transfer by way of the peripheral nerves to the central nervous system He sought diligently for pathological changes in the central nervous system but with his primitive methods saw only congestion

As to the treatment the variety and type of procedures and medicines show a strong bond with medieval mysticism They vary all the way from blood letting to a drink of blood galvanism magnetism and pressure on the carotids (p 511) There is given a list of some sixty medicaments of every conceivable sort with directions in "cookbook style on how to use them

3 EKSTROM Rabies epidemic at Stockholm in 1824 London M Gaz 6 689 1830

Cauterization of rabid dog bites has played such a prominent part in the history of treatment that this note is of considerable interest The treatment adopted consisted in making deep incisions in the wound and surrounding parts in different directions these were then diligently washed for several minutes either with water or with diluted muriatic acid or a solution of muriate of lime the wound being thoroughly cleansed was then dried and any remaining blood removed after which a hot iron or potassa fusa or in a few instances strong muriatic acid was applied always taking care to touch every point of the bottom of the wound and incisions so that a large eschar was formed" "Of the entire number" who "applied on being bitten only one afterwards suffered from the disease" Ekstrom thought that the local primary treatment" was "calculated to eliminate or to destroy the poison as soon as possible" Confidence in the method was shaken by the alleged cure of a patient with overt hydrophobia by excision and cauterization of the scar of the bite Follen Cabot ("Rabies and its preventive treatment an analysis of cases M News 74 321 1899) appears to have introduced cauterization (under an anesthetic) of the bite with nitric acid following some favorable experiments on guinea pigs Although cauterization with nitric acid was still used Webster (*op cit* p 88) concluded "What nitric acid does to rabies virus when applied to a wound inflicted by a rabid dog is not certainly known H J Shaughnessy and J Zichis (Prevention of experimental rabies" J A M A 123 528 1943) later explored the subject thoroughly and concluded "In experiments in which treatment of wounds contaminated with rabies virus was initiated within thirty minutes only 11 per cent of those treated with fuming nitric acid and only 6 per cent of

those treated with soap solution [20 per cent solution of soft soap] became infected compared with about 63 per cent of untreated controls" The application of treatment after 6 hours was definitely less effective than when it was given within 30 minutes

4 BOUCHARDAT [A] Rapport général fait à la demande 1 de M le ministre de l'intérieur de l'agriculture et du commerce 2 de M le ministre de l'instruction publique et des cultes 3 de M le ministre d'État par la commission permanent des remèdes secrets et nouveaux sur divers remèdes proposés pour prévenir ou pour combattre la rage Bull Acad de méd 18 6 1852 20 711 1851

Rabies was a very live subject in France during the middle of the nineteenth century Innumerable reports and discussions are recorded in the transactions of the various academies Bouchardat was commissioned to look into the questions of therapeutic claims and this long paper listed innumerable prescriptions for preventing or curing rabies Most of these are obviously fanciful such as the famous "cabalistic omelette"—eggs with ammonia served on oyster shells Bouchardat concluded "You will pardon this long and sterile enumeration but it is important to establish that in all of these claims there is nothing new and nothing useful We believe that we have shown that these formulas have lost their traditional prestige and that there remains nothing but ridiculous assertions without proof" Thus Bouchardat did a useful job and made a real advance over the days of Zinke (Ref 1) and Krugelstein (Ref 2)

5 TROUSSEAU A Clinique médicale de l'Hôtel Dieu de Paris Vol 2 De la rage p 342 2d ed Paris J B Baillière et fils 1865

The masterly clinical descriptions of Trousseau cannot be surpassed The following is from his lecture on rabies (p 357) "During the incubation period, there is no apparent departure from health and according to Van Swieten those who will later become rabid may contract the most diverse maladies such as smallpox, without the progress of the rabies being in any way modified When the period of incubation has lasted 2 or 3 months the man who has been bitten suddenly shows an unaccountable sadness The patient who usually does not suspect the nature of his trouble seeks diversion away from home but wherever he may be his sleep is unquiet agitated often he wakes with a start restlessness is continuous he draws long sighs he flees the friends who try to distract or to console him he takes pleasure in solitude and begs that no noise be made near him ministrations increase his restlessness and agitation

"Aggravation of these symptoms marks the beginning of the second period of the malady and at the same time other phenomena develop The patient complains of precordial distress respiration becomes sighing the pulse irregular These troubles with respiration and with circulation as well as the melancholy and agitation are the expression of an already considerable implication of the nervous system This situation becomes worse when the patients are taken with chills or veritable convulsions of all the muscles of the body Finally there appears a symptom practically constant in established rabies in man *the horror of water*

"The sight of this liquid often suffices to bring on a general tremor but it is above all, when the patient wishes to bring water to his lips that this special

horror comes on those convulsions of the face and of the entire body which make such a vivid impression on those who witness an attack The rabid man completely preserves his reason he is thirsty he wishes to drink, he bids his hand carry to his lips the vessel filled with liquid but no sooner does it touch him than the unhappy creature withdraws terrified sometimes he cries out that he cannot drink his face shows agony his eyes are fixed his features contracted then his limbs shake and his body quivers This crisis lasts several seconds gradually calm seems to return but the least contact even a breath of air suffices to start a new crisis such is the hypersensitivity of the skin. He cannot wash hands or face or comb his hair without being menaced by convulsions Some with hydrophobia are taken with abrupt terrors they turn suddenly thinking they hear someone talking to them They have indeed hallucinations of sight and hearing

"In the third that is to say the last stage other symptoms are added to those already present in increasing severity as the thirst becomes more acute and the impossibility of satisfying it more marked one observes a hoarseness of the voice first intermittent later constant this is probably the consequence of a spasm or of paralysis of some of the laryngeal muscles In the last hours of life the patient s mouth often fills with a white froth which is constantly ejected by coughing Meanwhile the convulsions become more and more frequent they no longer require anything to precipitate them, but recur spon taneously several times an hour The end of each convulsive bout is marked by a spasm of the respiratory muscles, with all the signs of an obstacle to breathing This spasm is prolonged with a final access and the rabid man dies of asphyxia *mors convulsiva cum summa in respirando angustia* "

Trousseau insisted that there was a specific virus in the saliva of the rabid animal which was the only means of transmitting the disease With the meth ods available he found no special anatomical lesions As to treatment he ad vised cauterization with a hot iron (*fer rougi*) raised the question of whether *curare* injected into the vein would help the spasm and finally gives a formula which the Chinese regard as infallible

Musc	16 grammes
Cinabre natif Cinabre factice	aa 20–

6 CALTIER V Etudes *sur* la rage Compt rend Acad d sc, 89 444 1879

Galtier reports that rabies is transmissible to the rabbit which acts as a harm less test object to tell whether saliva or other liquids come from a rabid animal He states that rabies is transmissible from rabbit to rabbit but does not give the method of inoculation The symptoms are paralysis and convulsions The average incubation period is 18 days

This appears to have been the first report on transmission to rabbits unfor tunately without much needed detail The work of Pasteur (Ref 7) was on the other hand definitive A little later Maurice Raynaud ("Sur la transmissi bilite de la rage de l'homme au lapin" Compt rend Acad d sc 89 714 1879) reported an observation in which saliva from a rabies patient was in jected subcutaneously into a rabbit s ear Four days later the rabbit was seized

with a sort of "accès de fureur" and died the following night Fragments of submaxillary gland introduced into other rabbits subcutaneously are said to have reproduced rabies as they died on the fifth and sixth days Autopsy showed only congestion of the lungs

These observations are not convincing They are mentioned because often cited as definitive for example "Raymond [*sic*] transmitted human rabies to rabbits" (Webster *op cit* p 46 Hogyes *op cit* p 35)

7 PASTEUR L. avec la collaboration de MM CHAMBERLAND ROUX et THUILLIER Sur la rage Compt rend Acad d sc. 92 1259 1881

At about this time many attempts were being made in France to transmit rabies from man to animal and from animal to animal and Pasteur s important studies began with this report His original paper ("Sur une maladie nouvelle provoquée par la salive d un enfant mort de la rage" Compt rend Acad d sc 92:159 1881) describing the injection into rabbits of saliva from a child dead of rabies clearly dealt with the production of pneumococcus septicemia (see "Pneumococcal Pneumonia" Ref 11) and not with rabies So too the observations of Raynaud and Lannelongue ("Recherches expérimentales sur la transmission du virus rabique de l'homme au lapin" Bull. Acad de med 10 61 1881) probably concerned "sputum septicemia" rather than rabies since the rabbits all died within 48 hours and there is no description of lesions Indeed, in the discussion of this paper Pasteur himself insisted that a bacterial infection had been produced Galtier on the other hand ("Observations à l occasion du procès verbal" Bull Acad de méd 10 90 1881) may have transmitted rabies from dog to rabbit, since the incubation period is reported as 12–18 days he also claims to have transmitted the disease from rabbit to rabbit and from rabbit to sheep but he was unable to produce rabies by injections of material from the central nervous system

Pasteur with his extraordinary acumen and experimental ability resolved the question in this report Both the symptoms and the histologic changes led Pasteur to the conclusion that "the central nervous system and especially the bulb which joins the spinal cord to the brain are particularly concerned and active in the development of the disease" He then reported success in pro ducing rabies by injection of central nervous system material and spinal fluid "The seat of rabies virus is not then solely in the saliva The brain contains it in virulence at least equal to that which it possesses in saliva" Pasteur was bothered by the experimental difficulties of the very long incubation period He soon found that by injecting cerebral substance from rabid animals directly into the brains of dogs the incubation period was shortened to 1 or 2 or at the most 3 weeks This was a radical advance in experimental rabies studies

8 PASTEUR L avec la collaboration de MM CHAMBERLAND ROUX et THUILLIER Nouveaux faits pour servir à la connaissance de la rage Compt rend Acad d sc 95 1187 1882

Pasteur reported further on his fundamental studies He pointed out that saliva was not a satisfactory source of virus for experimental work since its effects were uncertain and the incubation period might be very long He again re ferred to the certainty and rapidity with which rabies could be produced by

direct intracerebral injections of central nervous system material from rabid animals He pointed out that virus was found not only in the lower centers of the brain but in the spinal cord as well He differentiated "dumb" rabies (*rage mue*) featured by paralysis and "furious" rabies (*rage furieuse*) [1] He found that inoculation into the blood stream first affected the spinal cord and was likely to produce the "dumb" type rather than the "furious" He showed that an animal which recovered after early symptoms of rabies was immune to later inoculations and that some dogs seemed to have a natural resistance Finally, he produced rabies by intracerebral injection of all parts of the brain of a cow dead of rabies

9 PASTEUR [L] avec la collaboration de MM CHAMBERLAND et ROUX Nouvelle communication sur la rage Compt. rend Acad d sc 98 457 1884

Pasteur now made a more definitive report Intravenous injection as previously stated usually produced a paralytic type of rabies and dogs sacrified at the first symptom of paralysis showed spinal cords containing virus when there was no evidence as yet of any in the bulb He also demonstrated virus in the pneumogastric and sciatic nerves and in the salivary glands "The entire nervous system from center to periphery is then susceptible Virus preserved its virulence in spinal cords kept at 0 -12 C Pasteur was unable to cultivate any bacteria from the nervous system or the spinal fluid but he stated that "one is tempted to believe that a microbe of infinite smallness having the form neither of a bacillus nor of a micrococcus is the cause" He reported observations to show that the clinical type of rabies produced depended somewhat on the dose of infective material and he believed that injections of very small amounts of virus did not produce immunity He discussed the hypothesis of the passage of virus from the periphery to the central nervous system via the nerves as against the distribution of virus by the blood stream and whether or not the former was correct he regarded the latter as proved Finally and most important he discussed the theoretical basis of immunizing injections and made a general statement that he had already achieved some success A little later Pasteur (avec la collaboration de MM Chamberland et Roux "Sur la rage" *ibid* p 1229) made another communication to the academy dealing primarily with the problem of attenuation of virus If one passed rabies virus from dog to monkey and then from monkey to monkey the virulence of the virus fell off at each passage If the virus was then returned to dog rabbit or guinea pig it remained attenuated It did not immediately resume the virulence of street virus (*la rage des rues*) in the dog Even intracerebral inoculation might not produce the disease although it established nonetheless "a state refractory to rabies But if virus was passed from rabbit to rabbit the virulence became exalted so that if passed back to the dog it was much more virulent than street virus and inoculated into the blood stream it always caused fatal rabies By using a series of injections of attenuated virus he made dogs as stated immune or at least refractory He alluded in a general way to some favorable observations on immunization of man taking advantage of the

[1] Krugelstein (Ref 2) gives the classifications of older writers "The Englishman Mayerne describes seven forms of rabies"—the hod madness the running madness the fallen madness the sleepy madness etc

long incubation period He outlined plans for further experiments along these lines

10 PASTEUR L Méthode pour prévenir la rage après morsure Compt rend Acad d sc **101**:765 1885

Although Pasteur had alluded to his method of prophylaxis of rabies in previous papers he here first gave a detailed and comprehensive account The first step was the intracerebral inoculation of street virus into a rabbit and the passage through successive rabbits The incubation period gradually became shorter until it reached a fixed time of seven days The cords of rabbits of this sort contained virus throughout their extent which gradually diminished in viru lence as the cords were "suspended in dry air" The actual immunization was carried out by injecting into a dog subcutaneously a Pravaz syringe of broth to which was added a tiny bit of rabbit cord beginning with one dried long enough to be entirely avirulent and successively using more virulent material until "finally one reaches a last very virulent cord" The dog was by this time refractory to rabies as demonstrated in fifty animals At about this time there arrived from Alsace a boy of nine years Joseph Meister who had been bitten fourteen times by a rabid dog Drs Vulpian and Grancher examined the boy and thought that he surely had received a fatal inoculation with rabies "The death of this child seemed inevitable and I decided not without lively and cruel doubts as one can believe to try in Joseph Meister the method which had been constantly successful with dogs Consequently on July 6 at 8 in the evening 60 hours after the bites in the presence of Drs Vulpian and Grancher we inoculated under a skin fold in the right hypochondrium of the little Meister a half syringe of the cord of a rabid rabbit preserved in a flask of dry air for 15 days" Thirteen successive inoculations were made with cords of increasing virulence The little boy never developed rabies during a period of 3 months and 3 weeks

Pasteur with the penetrating curiosity which was so characteristic of him was not satisfied with practical results but wished to understand the mechanism of his method He concluded that the dried cords contained fewer and fewer live virus particles which were not, however attenuated in individual virulence Thus the method consisted in essence of injecting larger and larger quantities of virus each day

An interesting discussion followed the paper Vulpian said "Rabies that terrible malady against which all therapeutic attempts have so far failed has finally found its remedy Others expressed themselves with equal enthusiasm and Pasteur closed the meeting with gracious acknowledgment of what had been said

A little later Pasteur ("Résultats de l application de la méthode pour prévenir la rage après morsure" Compt rend Acad d sc **102** 459 1886) reported results of the treatment in three hundred and fifty cases Only one person developed rabies a child bitten on the third of October and not brought for treatment until November 9 According to contemporary statistics rabies should have developed in one sixth of those bitten In no case did the injections produce local inflammation abscess or other untoward effect Pasteur con cluded "The prophylaxis of rabies after bite is established It is time to create

a center for vaccination against rabies" A commission was appointed by the academy to help implement Pasteur s proposal The commission proposed that an establishment to be called the Pasteur Institute (*Institut Pasteur*) be founded for the treatment of both the French people and foreigners

Pasteur made further progress reports ("Note complémentaire sur les ré sultats de l application de la méthode de prophylaxie de la rage apres morsure" *ibid* **102** 835, 1886) Over seven hundred people had now been treated, including thirty eight Russians bitten by rabid wolves Three of this group died and Pasteur points out the great virulence of wolf bite compared to that of the dog

11 PASTEUR Louis Nouvelle communication sur la rage Compt rend Acad d sc **103** 777 1886

By this time the Pasteur treatment had become highly standardized There were ten daily injections of rabbit cord beginning with material dried for 14 days and concluding with the "5-day cord" Among seventeen hundred patients the treatment was ineffective in ten Although this figure was much lower than in untreated cases Pasteur was a little unhappy He noted that most of the fatal cases were children bitten about the face He was not sure that the treat ment was adequate for this type of case He decided to modify the procedure to make it more rapid and more effective He gave more injections three for example on the first day and continued treatments over a longer period of days The important point is that Pasteur himself now recognized that the treatment was not infallible

Detailed reports appeared each year from the Pasteur Institute In 1898 for example (H Pottevin "Les Vaccinations antirabiques à l'Institut Pasteur" Ann Inst Pasteur **12** 301 1898) there were reported a total of 20 166 per sons treated with 96 deaths or a mortality of 0 46 per cent Hogyes (*op cit*, p 237) gives an interesting list of reports from various treatment centers (Pasteur institutes) the world over

12 ROUX E Note sur un moyen de conserver les moelles rabiques avec leur virulence Ann Inst Pasteur **1** 87 1887

Roux found that specimens from rabid animals sent in for examination were often putrid It occurred to him to place the fresh material in glycerine in which the virus was not destroyed and he found that substance from the nervous system could be kept for 4 weeks at room temperature and still be virulent A Calmette following this suggestion ("Notes sur la rage en Indo Chine et sur les vaccinations antirabique pratiquées à Saigon du 14 avril au 1er août 1891" Ann Inst Pasteur **8** 633 1891) was able to keep a supply of desiccated cords preserved in glycerine on hand so as to be prepared at all times to give antirabic treatment Various other methods of "attenuating" rabies virus for vaccine have been devised such as that of G P Alivisatos ("Die Schutzimpfung gegen Lyssa durch das mit Aether behandelte Virus fixe" Deutsche med Wchnschr **48** 295 1922) who treated brain containing virus with ether with satisfactory results (See also Fermi Ref 17)

13 DI VESTEA A and ZAGARI G Sur la transmission de la rage par voie nerveuse Ann Inst Pasteur **3** 237 1889

There have been two main views as to the route whereby rabies virus reaches the nervous system (1) by the blood stream and (2) by the nerves Pasteur had shown (Refs 7 8) that inoculation by blood stream and intracerebral inoculation were effective Di Vestea and Zagari ("Compte rendu d une année d observations et d expériences sur la rage et sur la méthode de traitement préventif de Pasteur" Ann Inst Pasteur 1 492, 1887) brought forward clinical and experimental evidence that rabies virus was spread from the bite to the central nervous system by passage along nerves They had shown for example that inoculation of fixed virus into the sciatic nerve of a rabbit and of a dog caused death with the same symptoms as those of intracerebral inoculation Furthermore disease could be prevented by cutting and cauterization of the nerve after injection Finally the type of clinical phenomenon produced seemed to depend on the location of the inoculated nerve and where it entered the central nervous system Bardach ("Nouvelles recherches sur la rage" Ann Inst Pasteur 2 9 1888) came to similar conclusions E Roux (Notes de laboratoire sur la présence du virus rabique dans les nerfs" Ann Inst Pasteur 2 18 1888) agreed with these views but held certain reservations "One sees then, that inoculation into the nerves does not always produce rabies with the certainty of inoculation by trepanation" Meanwhile Nocard and Roux ("Expériences sur la vaccination des ruminants contre la rage par injections intraveineuses de virus rabique" Ann Inst Pasteur 2:341 1888) showed that large intravenous injections of rabid spinal cord could be given with impunity to sheep and goats although immunity was conferred C Helman ("Action du virus rabique" Ann Inst Pasteur 3 15 1889) concluded that rabies virus produced infection on inoculation only "if introduced directly into the nerve cells although if introduced into subcutaneous tissue it could give immunity" In the present paper Di Vestea and Zagari studied the subject further and concluded that "all cases of human rabies in which the symptoms are in accord with the site of the bite bear witness in favor of absorption of virus by the nervous route" All this shows how exceedingly complex and confused the subject was Recently Webster (Epidemiologic and immunologic experiments on rabies" New England J Med 217 187 1937) found that virus injected under the skin of Swiss mice is first detected 5 or 6 days later in the central nervous system at the site in direct connection with the inoculated areas This finding is consistent with "the view that the virus does travel by way of the nerves" But "virus cannot actually be detected in the peripheral nerves until it has been demonstrated in brain or cord In the mouse therefore we do not know just how the virus travels from the surface to the cord or brain"

14 NEGRI A Beitrag zum Studium der Aetiologie der Tollwuth Ztschr f Hyg u Infectionskr 43 507 1903 ("Contributo allo studio dell eziologia della rabbia" Boll della Soc med chir di Pavia 3 88 1903)

It is small wonder that Negri working in the laboratory of Golgi in Pavia where studies of malaria were being intensively pursued should regard the bodies which bear his name as living parasites "The finding to which I especially wish to draw attention is the occurrence of a specific micro-organism in the nervous system of rabid animals everything leads us to the conclusion that it should be included among the Protozoa" These alleged parasites were seen especially in the dog Negri observed them also in one human case The

site of predilection of the micro-organism is the horn of Ammon In this region, especially in the larger nerve cells the parasites are present in large numbers They exhibit the form of small sharply outlined structures" They were also found in spinal ganglia and in the spinal cords of dogs in which rabies occurred naturally or experimentally and in rabbits experimentally inoculated The bodies are of various size from 1 μ up to 10 12 or 15 μ or even as large as 27 μ by 5 μ They are stained best with eosin-methylene blue Four to six parasites may be found in one cell Negri thought that he saw evidences of multiplication of these bodies The many elaborate details of structure must be read in the original paper which also contains colored microphotographs of the bodies In another paper Negri (Zur Aetiologie der Tollwuth. Die Diagnose der Tollwuth auf Grund der neuen Befunde," Ztschr f Hyg u Infectionskr 44 519 1903) used the presence of "Negri bodies as a practical diagnostic test for a rabid animal and laid the ground for the method still regularly used today

The story of events leading to the discovery of the causal agent of rabies is one of great interest Pasteur himself (Ref 7) had speculated that the agent was a minute one unlike ordinary bacteria V Babes ("Studien über die Wuthkrankheit Virchows Arch f path Anat 110 562 1887) reviewed various claims of a bacterial agent and himself isolated several organisms from the nervous systems of rabid animals with cultures of which he claimed to reproduce rabies but interestingly enough he thought that the causal agent was a minute body perhaps carried in the bacteria Babes later ("Les Corpuscules de Negri et le parasite de la rage" Presse méd. 14 669 1906) confirmed the presence of Negri bodies in rabies but concluded that they represented a reaction to infection and were not parasites although they might contain them The causal agent Babes thought must be more widespread in the nervous system He concluded that it was a minute though visible body which could be stained as a dust" and which was found in degenerated cells through the nervous system These observations were elaborated a little later (V Babes "Untersuchungen uber die Negrischen Korper und ihre Beziehung zu dem virus der Wutkrankheit" Ztschr f Hyg u Infectionskr 56 435 1907) Two years later Negri ("Uber die Morphologie und den Entwicklungszyclus des Parasiten der Tollwut" Ztschr f Hyg u Infectionskr 63 421 1909) elaborately redescribed his bodies still insisting that they were parasites and pointing out that Calkins had named them *Neurocytes hydrophobiae* Calkins it should be remembered worked on the Guarnieri bodies of smallpox (see "Smallpox" Ref 3) and concluded that they too were living parasites Meanwhile P Remlinger ("Isolement de virus rabique par filtration" Compt rend Soc de biol 55 1433 1903) claimed to have produced rabies in rabbits with Berkefelt V filtrates of putrefied central nervous system material from rabid dogs and rabbits Finally J Koch and P Rissling ("Studien zur Aetiologie der Tollwut" Ztschr f Hyg u Infectionskr 65 85 1910) described small coccus like bodies in the gray matter of the central nervous systems of rabid dogs which they thought might be of etiological significance Like Babes they did not accept the Negri bodies as parasites Later confirmation of the filtrability of rabies virus of course rules out the bodies of Negri and of Koch as causal agents, whatever diagnostic value they may have The subject of the

Negri bodies is critically reviewed by P Frosch ("Lyssa" in W Kolle and A Wassermann *Handbuch der pathogenen Microorganismen* Vol I Erganzungsband [1907] p 626) The nodules described by Babes (Sur certains caractères des lésions histologiques de la rage" Ann Inst Pasteur 6 209 1892) which seem to be leukocytic accumulations in relation to blood vessels are now thought to be common to neurotropic virus infections Indeed the Negri body is perhaps the only absolutely specific anatomical change T F Sellers ("A new method for staining Negri bodies of rabies" Am J Pub Health 17:1080 1927) developed a useful method of demonstrating Negri bodies by impression preparations of brain tissue specially stained

15 REMLINGER P Accidents paralytiques au cours du traitement antirabique Ann Inst Pasteur 19:625 1905

This is the first comprehensive discussion of the paralyses occurring in connection with antirabic therapy Remlinger gives abstracts of all the reported cases—26 in number—beginning in 1888 He analyzes the whole problem and discusses various explanations including the introduction of non viral toxic substances He finally leans toward a "rabic toxin" as the explanation (see also Ref 19)

16 FERMI Claudio Ueber die Virulenz des Speichels und der Speicheldrusen wutkranker Tiere Centralbl f Bakt 44 26 1907

Although Zinke (Ref 1) a century earlier had given evidence that rabies virus is present in saliva it is amazingly difficult to demonstrate it experimentally Fermi discusses the discordant results of various investigators and reports extensive observations of his own on the intracerebral and subcutaneous injection of saliva from all sorts of rabid animals into test subjects In a huge number of experiments rabies was never produced E Bartarelli ("Ueber die Wege auf denen das Wutvirus zu den Speicheldrusen des Hundes gelangt," Centralbl f Bakt 37 213 1904) on the other hand seemed to show that virus reached the salivary glands in rabid dogs by peripheral travel along nerves His demonstration consisted in severing first the nervous and then the vascular connections of the parotid gland after which the animal was inoculated with rabies virus emulsion The glands from animals in which the nervous but not the vascular connections were preserved produced rabies in other animals Meanwhile Roux and Nocard ("A quel moment le virus rabique apparait il dans la bave des animaux enragés?" Ann Inst Pasteur 4 163 1890) showed that rabies virus could be found in the saliva of rabid dogs 2 or 3 days before the least clinical symptoms J Nicholas later ("Apparition de la virulence dans la salive mixte des animaux rabiques" Compt rend Soc de biol 60 625 1906) found saliva virulent as long as 6 days before the animal showed any recognizable clinical signs of rabies

17 FERMI Claudio Ueber die Immunizierung gegen Wutkrankheit Ztschr f Hyg u Infectionskr 58 232 1908

Fermi reviews comprehensively the previous methods of vaccination including Pasteur s and points out various defects He introduced a new method in which the vaccine was treated with carbolic acid One hundred per cent of test animals were saved whereas 100 per cent of untreated controls died He mentions

as advantageous "uniformity of the vaccine and simplicity of preparation instead of the complicated and useless Pasteur method of attenuation" This vaccine can be preserved and sent anywhere so as to be always available Later in a masterful article on the practical aspects of rabies Sir David Semple ("On the nature of rabies and antirabic treatment Brit M J 2 333 371 1919) described a method for preparing a dead carbolized vaccine and reported the cases of 2 009 Europeans in India who were treated with only 0 19 per cent of failures If immunization is complete before the virus traveling along peripheral nerves reaches the central nervous system the patient survives otherwise he dies Hence mild bites at the periphery with a long incubation period are more favorable for immunization than severe bites on the face with a brief incubation L T Webster ("The immunizing potency of antirabies vaccines a critical review Am J Hyg 30 113 1939) gives an elaborate review of all the reported laboratory experiences in rabies vaccination He concludes "All workers save Fermi have failed to demonstrate a significant protective effect of vaccination *following* experimental exposure to rabies virus by any route" On the other hand vaccine virulent or non virulent given *before* exposure has been found effective under limited conditions These rather gloomy conclusions do not seem in harmony with reports of human vaccination (Ref 25)

18 STUART G and KRIKORIAN K S The neuro paralytic accidents of anti rabies treatment Ann Trop Med 22 326 1928

That paralysis occurred in a certain number of instances during or following antirabic vaccination was an unquestioned fact (Ref 15) A debate went on for years as to whether these accidents represented rabies from the bites of the rabid animal or whether in cases where the animal turned out not to be rabid atypical rabies was produced by rabies virus in the vaccine

E Centanni ("Sui prodotti tossici secondarii nelle infezioni Riforma med 3 637 1898) and A Aujeszky ("Ueber Immunisierung gegen Wut mit normaler Nervensubstanz" Centralbl f Bakt 27 5 1900) thought that it might be possible to produce immunity to rabies by injections of *normal* nervous system material They found the animals did badly lost weight developed skin abscesses and sometimes died but no paralytic accidents are mentioned Eduard Muller ("Ueber acute Paraplegien nach Wutschutzimpfungen" Deutsche Ztschr f Nervenh 34 252 1908) in the course of a masterful description of paralytic accidents following rabies vaccine stated "A further possibility is the fact that in the Pasteur treatment not insignificant amounts of foreign and diseased spinal cord substance are introduced subcutaneously into the human body He did not however make any experimental observations P Remlinger ("Accidents paralytiques d origine médullaire provoqués chez le lapin par des inoculations de substance nerveuse normale homologue" Compt rend Soc de biol 83 171 1920) first produced paralysis in a healthy rabbit by injections of brain from a normal rabbit He points out the rarity of this finding but notes "This fact is interesting from the point of view of the paralyses which sometimes occur in man in connection with Pasteur therapy" Fritz Schweinburg ("Klinische und experimentelle Beobachtungen uber Lahmungen nach Wutschutzimpfung" Wien klin Wchnschr 37 797 1924) reported similar findings Stuart and Krikorian in an article definitive to date

concluded that "in the basic nerve substance of all antirabic vaccines there seems to exist some deleterious component which is capable of producing neuro-paralytic disorders" They then actually showed that "paralytic accidents can be produced experimentally by the repeated inoculation of nerve substance normal or rabid homologous or heterologous" Later T M Rivers D H Sprunt and G P Berry ("Observations on attempts to produce acute disseminated encephalomyelitis in monkeys" J Exper Med 58:39 1933) showed that repeated intramuscular injections of brain extracts and emulsions into monkeys might be followed by an inflammatory reaction with demyelinization Similar findings were described by E A Kabat A Wolf and A E Bezer ("The rapid production of acute disseminated encephalomyelitis in rhesus monkeys by injection of heterologous and homologous brain tissue with adjuvants" J Exper Med 85:117 1947) and by Isabel M Morgan ("Allergic encephalomyelitis in monkeys in response to injection of normal monkey nervous tissue" J Exper Med 85 131 1947) A good modern summary of the subject is that of L Weinstein and M Goldfield ("Reactions to rabies vaccine with a report of two cases of encephalomyelitis Boston M Quart 4 7 1953) Statistics are given in the paper by E Appelbaum M Greenberg and J Nelson ("Neurological complications following antirabies vaccination" J A M A **151** 188 1953) and in McKendrick s review (Ref 25)

Recently J F Bell J T Wright and K Habel ("Rabies vaccine freed of the factor causing allergic encephalitis" Proc Soc Exper Biol & Med 70 457 1949) have tried to reduce the danger of neurological accidents by removing from vaccine the encephalitis-causing factor

19 REMLINGER P La Rage de laboratoire Bull Acad de méd Paris **113** 836 1935

It had long been noted that various "paralytic" accidents were associated with antirabic therapy There might be a Landry like ascending paralysis signs of a lumbodorsal myelitis or peripheral palsy of the seventh or fifth cranial nerve It had been assumed that these accidents were true rabies of a type different from the spontaneous disease—laboratory rabies (*la rage de laboratoire*) This term was first used by Chauveau in a discussion of Peters paper (Inoculations antirabiques intensives et mort par la rage" Bull Acad de méd Paris **17** 16 1887) in which he questioned the value of antirabic vaccination (Pasteur) and created a violent discussion which went on for months in the academy (*ibid* pp 28 72) Remlinger in this paper discusses the question of whether these accidents of therapy are actually rabies especially the mild non fatal ones No final answer was reached although he concluded that "with the exception of certain paralyses following dead vaccine the accidents of antirabic therapy are largely due to fixed virus (But see also Ref 15)

20 WEBSTER L T and DAWSON J R Jr Early diagnosis of rabies by mouse inoculation Measurement of humoral immunity to rabies by mouse protection test Proc Soc Exper Biol & Med **32** 570 1935

The early literature on infection of mice with rabic virus is reviewed by A Hoyt and C W Jungeblut ("Experimental rabies in white mice and attempted chemotherapy J Infect Dis 47 418 1930) but to obtain useful results Webster and Dawson found it necessary to breed mice specially for high

susceptibility to neurotropic viruses Using such animals they found that rabies was readily produced by intracerebral inoculation of fresh dog brain containing Negri bodies This brief experience suggests that rabies may be diagnosed within 7 days They also developed a mouse protection test for the quantitative measurement of protective antibodies against rabies Webster soon elaborated this material in another paper (Diagnostic and immunologic tests of rabies in mice" Am J Pub Health 26 1207 1936), and finally ("A mouse test for measuring the immunizing potency of antirabic vaccines" J Exper Med 70 87, 1939) Webster using the mouse test was able to appraise the potency of vaccines showing that "virulent virus injected intraperitoneally as a vaccine, immunized mice within 10 days and for a period of at least 9 months Demonstrable neutralizing antibodies accompanied this immunity Virus subcutaneously failed to immunize as effectively" Commercial vaccines containing virulent virus gave results similar to those obtained with laboratory virus but commercial vaccine inactivated with phenol generally failed to immunize mice It is interesting that various commercial vaccines varied greatly in their immunizing potency Similar results were obtained in dogs (L T Webster and J Casals A dog test for measuring the immunizing potency of antirabies vaccines" J Exper Med 71 719 1940) Confirmatory experiments were also reported by R W G Wyckoff and C E Beck ("The potency of anti rabic vaccines J Immunol 39 17 1940) Charles N Leach ("Comparative methods of diagnosis of rabies in animals, Am J Pub Health 28 162 1938) confirmed the practical value of Webster s mouse test and indeed found it positive in 12 per cent of brains reported negative for Negri bodies (Ref 14) whereas only 3 specimens among 338 reported positive gave a negative mouse test K Habel and J T Wright ("Some factors influencing the mouse potency test for rabies vaccine Pub Health Rep 63 44 1948) developed a test for the immunizing potency of commercial vaccine

21 PAWAN J L Rabies in the vampire bat of Trinidad, with special reference to the clinical course and the latency of infection Ann Trop Med 30 401 1936

A carrier state is so common with viral infections that one naturally inquires whether there are asymptomatic carriers of rabies virus The vampire bat of Trinidad has definitely been shown to be such a carrier The earlier phases of this interesting story are told by E W Hurst and J L Pawan ("An outbreak of rabies in Trinidad without history of bites and with the symptoms of acute ascending myelitis" Lancet 221 622 1931 A further account of the Trinidad outbreak of acute rabic myelitis histology of the experimental disease" J Path & Bact 35 301 1932) In 1936 Pawan ("The transmission of paralytic rabies in Trinidad by the vampire bat [*Desmodus rotundus murinus* Wagner 1840]" Ann Trop Med 30 101 1936) first showed that human beings bitten by vampire bats develop sensory symptoms at the bitten site followed by paralysis and death and that the bats were definitely infected Finally in the present paper Pawan demonstrated that vampire bats might become carriers of rabies after "recovery" from the furious form of the disease In this state while apparently well they may remain capable of spreading infection by their bites for prolonged periods

22. WEBSTER L T and CLOW A D Propagation of rabies virus in tissue culture and the successful use of culture virus as an antirabic vaccine Science 84:487 1936

Webster and Clow first succeeded in growing rabies virus in tissue culture The medium consisted of Tyrode solution containing normal monkey serum plus a suspension of minced mouse embryo brain The inoculum consisted of brain from a mouse prostrate on the seventh or eighth day following an intra cerebral injection of rabies virus Material was passed through such culture medium as often as 88 times and the supernatant was still found to be virulent unless neutralized by sera from persons given Semple antirabic vaccine In order to get away from the adverse effects of injection of brain or cord material implicit in the older vaccine the supernatant culture fluid was used and was found highly effective when injected intraperitoneally making the mouse re sistant to 100 intracerebral fatal doses of street virus Webster and Clow soon published a more elaborate account of these studies ("Propagation of rabies virus in tissue culture" J Exper Med 66:125 1937)

23 GALLOWAY I A and ELFORD W J The size of the virus of rabies ("fixed" strain) by ultrafiltration analysis J Hyg 36:532 1936

Remlinger (Ref 14) made early studies on the filtrability of rabies virus Later Galloway and Elford, using graded collodion membranes assigned a diameter of 100–150 mμ to the virus of rabies Thus it falls among the larger viruses poliomyelitis particles for example being one fifth as large

24 BERNKOPF H and KLIGLER I Characteristics of a fixed rabies virus cultivated on developing chick embryos Proc Soc Exper Biol & Med 45:332 1940

Two groups of workers (I J Kligler and H Bernkopf "Cultivation of rabies virus in developing chick embryo" Nature 143 899 J R Dawson Jr "Infection of chicks and chick embryos with rabies" Science 89 300 1939) succeeded at about the same time in growing rabies virus in the chick embryo Kligler and Bernkopf inoculated the chorio-allantois Dawson the brain of the embryo In this paper Bernkopf and Kligler describe their work more in detail and point out that the chick embryo virus after many passages showed greatly reduced virulence for rabbits Dawson ("A study of chick-embryo-adapted rabies virus" Am J Path 17 177 1941) also found the virulence reduced for the rabbit and pointed out other interesting implications from the stand point of rabies infection and immunity H Koprowski and H R Cox ("Studies on chick embryo adapted rabies virus I Culture characteristics and pathogenicity" J Immunol 60 533 1948) among others developed this subject further

25 McKENDRICK A G A ninth analytical review of reports from Pasteur institutes on the results of anti rabies treatment League of Nations Bull World Health Organ 9 31 1940–41

As rabies is up to the present an incurable disease there has been tremendous emphasis on preventive measures The early work of Pasteur and others has already been mentioned (Ref 10) McKendrick gives a definitive review of

the various methods of prophylactic therapy he lists the methods which can be divided into injections of attenuated live virus (Pasteur) or of virus killed by phenolization or some other method Among 1 062 707 persons treated there was an over all mortality of 0 33 per cent Every conceivable factor was taken into account in the breakdown of the figures such as severity of the bite position intervention of clothing and delay in commencing treatment Paralytic accidents with various methods are discussed In general, there seems little choice between most of the methods although after wolf bites the mortality is 6 78 as against 0 26 with dog bites Deep bites as against superficial bites on head as against leg and delay in starting treatment are all unfavorable factors However all this complicated material must be consulted in the original Webster (*Rabies* p 100) gives a penetrating analysis of McKendrick s figures and concludes that they do not definitely answer the question of whether vaccine does or does not protect against rabies In practice however he feels strongly that antirabic therapy should be used in certain groups of cases such as those bitten through the skin by a dog proved rabid

G Proca and S Bobes ("Anti rabic immunization living vaccines and killed vaccines League of Nations Bull World Health Organ 9 79 1940-41) further analyze the problem They point out that "the harmlessness of live vaccines [Pasteur] is not a rule with no exceptions On the other hand Fermi s carbolized vaccine (Ref 17) behaves like an avirulent chemical vaccine when injected subcutaneously Moreover intracerebral inoculation of rabbits with larger doses may occasionally still produce rabies so that, clearly every virus particle is not definitely killed The authors incline to the use of chemical vaccines as being safer but feel that the final word is not yet said The problem seems similar to that of the Salk vaccine for poliomyelitis it is a question whether a completely killed vaccine retains full immunizing power

26 KOPROWSKI Hilary Experimental studies on rabies virus Canad J Pub Health 40 60 1949

It is not possible in this bibliography to go into all the details of control measures against rabies—muzzling quarantining etc These are fully discussed in the general references given at the beginning of this article We shall refer however to the question of protecting dogs by immunization S Umeno and Y Doi ("Antirabic inoculation of dogs and results of its protective application" Kitasato Arch Exper Med 4 89 1921) first prepared such a vaccine which was used with success in dogs in single doses H Koprowski has recently reviewed the subject He tried to produce a single injection" method for immunization of dogs by means of an egg passage virus Potent antirabies serum was also obtained from rabbits which Koprowski believed useful in both animal and human rabies as a supplement to vaccination Later Koprowski with J Van der Scheer and C E and J Black ("Use of hyperimmune antirabies concentrates in experimental rabies Am J Med 8 412 1950) found that one injection of hyperimmune antiserum protected small animals which had been infected 24 hours previously with street virus In contrast 14 injections of rabies vaccine begun 24 hours after exposure failed in all instances to protect They believe that antiserum plus vaccine should be applied in all cases of exposure to rabies

Section 28

YELLOW FEVER

YELLOW FEVER

IT SEEMS natural that so dramatic and picturesque a disease as yellow fever and one for a long time so puzzling should have been much written about. The history of the subject is well covered in Henry Rose Carter's scholarly book *Yellow Fever* (Baltimore Williams & Wilkins Co 1931) to which is appended an extensive bibliography George Augustin's huge volume *History of Yellow Fever* (New Orleans Searcy & Pfaff Ltd, 1909) also contains much interesting though undocumented material Extensive historical bibliographies are to be found in the works of La Roche (Ref 3) and of Hirsch (Ref 5) and the recent literature is well covered in Strode's monograph (Ref 29) There is an immense number of books dealing often dramatically with individual epidemics in some of which are listed in ghoulish detail the names of the many hundreds who died of the disease for example J M Keating *The Yellow Fever Epidemic of 1878 in Memphis Tennessee* (Memphis Printed for the Howard Association 1879) Of special interest is the book edited by Chauncey D Leake *Yellow Fever in Galveston Republic of Texas 1839* (Austin University of Texas Press 1951) which contains admirable brief "stories of the men who conquered yellow fever" and finally there is a readable account of the whole subject in H Harold Scott *A History of Tropical Medicine* (Baltimore Williams & Wilkins Co 1939) Vol 1, chap vii "Yellow Fever" page 279

1 RUSH Benjamin An account of the bilious remitting yellow fever as it appeared in the city of Philadelphia in the year 1793 2d ed Philadelphia Thomas Dobson 1794

We may well open this bibliography with an account of yellow fever by one of the outstanding physicians of the time However Rush's thinking and description are definitely oriented to the eighteenth century and actually are of little value except as historical material "The causes which induced indirect debility were 1 Fatigue of body or mind induced by labour It was labour which excited the disease so universally among the lower class of people A hard trotting horse brought it on two of my patients A fall excited it in a girl 2. Heat from every cause but more especially heat of the sun was a very common exciting cause of the disorder In addition intemperance fear grief cold etc were assigned as precipitating causes (pp 29 ff) The clinical description is based on the humoral theory of disease "The blood vessels are the seat and throne of this as well as of all other fevers I have publickly taught for several years that a fever is occasioned by a convulsion in the arterial system" (p 40) Rush goes on to describe in great detail the pulse and other features of the disease without of course any adequate physical examination "There were for several weeks two sources of infection viz exhalation and contagion The exhalation infected at a distance of three and four hundred yards, while the contagion infected only across the streets" (p 104) As to the causes which checked the disorder "On the fifteenth of October it pleased God to alter the state of the air The clouds at last dropped health in showers of

rain The appearance of this rain was like a dove with an olive branch in its mouth to the whole city" (p 130) The discussion of treatment is fanciful and need not be described in detail (pp 193 ff) There are elaborate and controversial arguments about the place in therapy of purging bloodletting blisters etc Rush came to feel that the disease was not contagious and in his *Medical Inquiries and Observations* (3d ed Philadelphia Benjamin & Thomas Keith etc. 1809) 4 235-84 he has a long section giving his reasons in detail. Of course the truth of the matter is that yellow fever *is not* contagious although rapidly transmitted by the mosquito about which Rush knew nothing at the time

Rush was undoubtedly a great man and a great physician in his day but we must think of him as an exponent of eighteenth-century medicine and not of the views developed in France at the turn of the century

A graphic account of this epidemic is given by W S Middleton, "The yellow fever epidemic of 1793 in Philadelphia" Ann M Hist 10 434 1928 and by J H Powell *Bring Out Your Dead The Great Plague of Yellow Fever in Philadelphia in 1793* (Philadelphia University of Pennsylvania Press 1949) With regard to Rush and his ideas on yellow fever see C E. A Winslow *The Conquest of Epidemic Disease* (Princeton N J Princeton University Press 1943) chap xi "The Enigma of Yellow Fever" page 193

2. LOUIS P Ch A Anatomical pathological and therapeutic researches on the yellow fever of Gibraltar of 1828 Translated from the manuscript by G C Shattuck Jr M D Boston Charles C Little & James Brown 1839 (Precedes the French edition)

Once more, as in the case of his book on typhoid fever one must pay homage to Louis for his cool objectivity in handling the facts and for his clear analysis of results Louis was of course an outstanding member of the young group of French clinician pathologists at the beginning of the nineteenth century who revolutionized and modernized the study of disease Louis with Chervin and Trousseau were sent to Gibraltar as a commission by the French government to study the epidemic of yellow fever then rampant Louis set out to do autopsies on fatal cases with meticulous care these were correlated with objective clinical findings The descriptions are masterpieces of clarity and precision and would do credit to a modern medical service or autopsy room Anatomically Louis soon centered his attention on the liver "But the most remarkable lesion of the liver was the alteration of its color This alteration consisted in a discoloration the liver being sometimes the color of fresh butter sometimes of a straw color sometimes of the color of coffee and milk etc." (p 117) Later in interpreting the lesions "Lesions apparently slight may explain death when they have taken place rapidly as in the cases now under consideration And then again in the present state of science we can not appreciate the nature of the specific lesion of the liver and consequently we can not determine how far it had anything to do with death" (p 144) "As then a strict analysis proves the existence of a cause unequal in its operation and of which but one effect is constant the specific alteration of the liver and as in a third part of the cases it is directly to this cause that we are obliged to refer death we naturally ask how does this cause act through the medium of what system does it

exert its influence on the economy? (p 164) But the objective Louis speculates no further he simply assembles evidence and waits He shows later by extensive statistics that yellow fever confers an immunity to a second attack even after a lapse of many years As to treatment he compares that of the English and the Spanish physicians at Gibraltar "It is true that in the army the ratio of mortality was one in four and a half and that in the city it was only one in six so that all other things being equal it would seem to result from these two principal classes of facts either that the treatment of the Spanish physicians was very efficacious or that of the English physicians was very injurious" (p 330)

The translator in his Introduction says this about Louis "Some seem to have been misled by the term numerical system which has been said to be that of M Louis They seem to have thought that his peculiarity consists in this merely that he counts We call some experienced scientific Is it not by comparing individual cases, by adding what they have observed in one to what they have observed in another by *counting* that they have become so?" (p xii)

3 LA ROCHE R. Yellow fever considered in its historical pathological etiological and therapeutical relations 2 vols Philadelphia Blanchard & Lea 1855

This monumental treatise deals with every phase of the subject which is made vivid by innumerable allusions to the literature and to the opinions and actions of individual physicians as well as commissions boards of health etc It opens with a bibliography of over a thousand titles presumably definitive to date The next section of some hundred pages deals with the various Philadelphia outbreaks Symptoms and clinical features are then discussed in minute detail (pp 129–383) after which comes a chapter on the pathological anatomy of the disease As to the liver "The secreting cells were pale ill defined and less granular than when in the normal state In the cells with few exceptions no nucleus could be detected The incubation period was regarded for the most part as from 3 to 6 days Dr Harrison of New Orleans remarks that persons who arrive in that city during an epidemic from the healthiest regions are subject to attack on the sixth fifth fourth or even as early as the third day after their arrival" a finding which indicates the promptness with which people were likely to be bitten by mosquitoes in an infected area There is next an analysis of the mortality of yellow fever (pp 513–46)

Volume 2 deals largely with the questions of etiology and contagion There was of course no idea of a living virus or of any part played by mosquitoes Among various circumfusa" which we now know have nothing to do with the disease such as light electricity and atmospheric pressure the writer was quite clear as to the relation to temperature The yellow fever is undeniably a disease of hot climates and hot seasons As to the immediate cause much diversity of opinion has existed relative to the nature of the efficient cause of yellow fever—to the sources whence that cause is derived—as well as to the mode of diffusion of the disease after it has once made its appearance By one set of physicians the disease is regarded as the offspring of a morbid poison found and elaborated in a diseased body and is invariably referred to importation from abroad By others "the fever has been invariably referred to the

evolution under particular circumstances both terrestrial and meteorological of a febrile poison originating in molecular changes independent of the arrival of vessels from sickly ports" (2:190) The major portion of this volume is then devoted to an intensive discussion of contagion versus non contagion to the latter of which the author adheres He tells how important physicians have changed from contagionists to non-contagionists "Dr Rush who as we have seen had originally espoused the cause of contagion at last relinquished his former views Not satisfied with doing so silently this eminent physician published a formal recantation"[1] (2:253) However there was a common belief that the disease arose by "infection" with a "miasma" and interestingly enough many analogies with malaria were noted "It is like other miasmal diseases under the influence of atmospheric vicissitudes It is limited in the sphere of its prevalence never extending beyond certain boundaries attacking those who venture within those boundaries even in the absence of the sick, and sparing those who keep aloof To these limits it may be restricted by a cessation of intercourse while the disease is arrested in its progress by the dispersion of the inhabitants of the infected localities and by preventing further access to these by artificial means" (p 595) Under the subject of prophylaxis it is necessary to effect the removal of all local nuisances before the accession of hot weather whereas docks or other localities liable to be visited by the disease courts yards gutters cellars should be left perfectly clear all accumulations of filth and stagnant water should be carefully removed streets courts and alleys should be paved The holds of vessels must be left clean and pure and all foul bilge water carefully pumped out" (2:732) The author however opposed quarantine both because he thought it useless and because of inconvenience to individuals and commercial losses (*ibid* p 737) "Much more useful will it be to obtain at once the complete evacuation of all the inhabitants of infected spots" (*ibid* p 749) Under treatment a fantastic list of agents is discussed—bleeding, local depletion emetics purgatives mercury diaphoretics sedatives oxide of bismuth rhatany tannin creosote adrue nitrate of silver lime water chloroform opium external applications affusions drinks injections cool air sinapisms moxa actual cautery Peruvian bark sulphate of quinia oil melambo charcoal moral treatment and diet

4 MACDONALD J Dennis Yellow fever a system of medicine 1 475 Edited by J Russell Reynolds Philadelphia J B Lippincott & Co 1868

A standard account of the disease shortly before the bacteriological era shows little recent advance in knowledge The author states that the infectious nature of yellow fever is now generally admitted He is unclear however as to how the disease *is transmitted and goes definitely wrong when he says that* "the clothing of infected persons or of healthy persons having communicated with infected places or persons may impart infection to other places or persons"

[1] "To prevent recurrence of the fever I early pointed out the domestic origin In this opinion I was opposed by nearly the whole College of Physicians who derived it from a foreign country and who believed it to be a specific disease They were followed by nearly all the citizens of Philadelphia (*The Autobiography of Benjamin Rush* ed George W Corner [Princeton, 1948] p 97)

The whole question of anticontagionism is thoroughly discussed in Erwin H Ackerknecht's "Anticontagionism between 1821 and 1867 Bull Hist Med 22 562 1948

Under treatment are mentioned the usual congeries of drugs "Acetate of ammonia nitrate of potash nitrous ether and tincture of squills and henbane may be combined with lime juice for a drink"

An authoritative modern discussion of the clinical aspects and diagnosis of yellow fever is that of J Austin Kerr in Strode (Ref 29 pp 381 ff) In this article the findings of various clinical laboratory tests are also summarized

5 HIRSCH August Handbook of geographical and historical pathology, 1 316, chap viii, 'Yellow Fever Translated from the second German edition London New Sydenham Society 1883

This is the great storehouse of information about epidemics of yellow fever, which are listed in detail as to time and place It is pointed out that yellow fever rarely occurs as a pandemic and that epidemic outbreaks never happen suddenly, a series of isolated cases always precedes them Often the disease remains limited to one quarter of a town The duration of epidemics varies greatly Many other circumstances of outbreaks are discussed Hirsch regards it as shown that yellow fever is communicable it is not now a question of whether communication actually takes place but only of how it takes place" Difference of opinion on this point "depends not so much upon conflicting facts but rather the significance ascribed to them There is of course no mention of the mosquito

The article is followed by a lengthy bibliography

6 FINLAY Carlos J The mosquito hypothetically considered as the agent of transmission of yellow fever Tran lated by Dr Finlay from the Anales de la Academia de ciencias médicas fisicas y naturales de la Habana **18** 147 1881 *In* Trabajos selectos del Dr Carlos J Finlay Havana Republica de Cuba, 1912

To Finlay seems to belong the credit for first clearly insisting that the mosquito was the vehicle for transmission of yellow fever [2] "I feel convinced that any theory which attributes the origin and the propagation of yellow fever to atmospheric influences to miasmatic or meteorological conditions to filth or to neglect of general hygienic precautions must be considered as utterly indefensible

I shall not concern myself with the nature or form of the morbific cause of yellow fever beyond postulating the existence of a material transportable substance which may be an amorphous virus a vegetable or animal germ a bacterium etc but at any rate constitutes something tangible which requires to be conveyed from the sick to the healthy before the disease can be propagated" He then enumerated the reasons which made him select the mosquito as the only suitable vector Finlay postulated that the mosquito carried the virus from

[2] The long rambling article by Josiah C Nott (Yellow fever contrasted with bilious fever—reasons for believing it a disease sui generis—its mode of propagation—remote cause probable insect or animalcular origin New Orleans M & S J 4 563 1848) to whom credit is often given for first claiming that yellow fever is transmitted by the mosquito is thus criticized by Ronald Ross (*Memoirs* [London John Murray 1923]) "Speculations of this kind are apt to be much overrated by penmen It is easy for persons to sit in arm-chairs and weave hypotheses many imagined America before Columbus but an ocean had to be traversed between the dream and reality Theorists who do not trouble to verify their own speculations deserve little credit" (p 424)

one person to another on the mouth parts He attempted five inoculations by means of mosquito bites with equivocal results He concluded "Should it finally be proven that the mosquito-inoculation not only reproduces the yellow fever but that it constitutes the regular process through which the disease is propagated the conditions of existence and of development for that dipterous insect would account for the anomalies hitherto observed in the propagation of yellow fever"

Apparently Finlay did not stimulate anyone to further investigation at the time and of course his idea that the virus was mechanically transported was incorrect had he known that the infective period of yellow fever lasts for only 3 or 4 days and that the mosquito must carry the virus for about 12 days before its bite becomes dangerous he might actually have solved the problem None theless he deserves full credit for pushing the idea of mosquito transmission Later ("Yellow fever its transmission by means of the Culex mosquito" Am J M Sc 92:394 1886) he described in interesting fashion the feeding habits of local mosquitoes and reported more transmission experiments which again did not seem to convince anyone But Finlay continued to expose his views as for example in a systematic discussion "Yellow fever" Edinburgh M J 10:35 1894 and in many papers some of which are controversial reprinted in *Selected Papers*

Finlay's life and work are sympathetically appraised by Carlos E Finlay *Carlos Finlay and Yellow Fever* (New York Oxford University Press 1940)

7 SANARELLI J Étiologie et pathogénie de la fièvre jaune Ann Inst Pasteur 11:433 673 1897

With the development of the bacteriological era many physicians became convinced that yellow fever was caused by a living germ As was the case with almost all infectious diseases reports poured in of claims for one or another bacterial agent. The early claims are concisely summarized in *Carlos Finlay and Yellow Fever* (Ref 6) only to be demolished by George M Sternberg (*Report on the Etiology and Prevention of Yellow Fever* [Washington Government Printing Office 1890]) who states in his conclusions "The specific infectious agent in yellow fever has not been demonstrated The most approved bacteriological methods fail to demonstrate the constant presence of any particular microorganism in the blood and tissues of yellow fever cadavers" (p 221) However Sanarelli's long paper was so emphatic with its report of isolating a specific bacterium *Bacillus icteroides* both from living patients and at autopsy and of the reproduction of lesions compatible with those of yellow fever in small animals that many were convinced for some years Sodré and Couto for example in their authoritative treatise on yellow fever (*Das Gelbfieber* [Vienna Alfred Holder 1901]) accept the organism of Sanarelli without reservation (pp 63 ff) An abbreviated translation of Sanarelli's paper also appeared in English ("A lecture on yellow fever" Brit M J 2 7 1897) But soon there after Reed and Carroll of the United States Army undertook to study *B icteroides* Reed was particularly well qualified having worked on hog cholera with Welch at Johns Hopkins In their first paper (Walter Reed and James Carroll "Bacillus icteroides and Bacillus cholerae suis a preliminary note" M News 74 513 1899) they gave cultural and experimental data for considering Sanarelli's organism as simply a variety of the hog-cholera bacillus Sanarelli un

Under treatment are mentioned the usual congeries of drugs "Acetate of ammonia nitrate of potash nitrous ether, and tincture of squills and herb ne may be combined with lime juice for a drink"

An authoritative modern discussion of the clinical aspects and diagnosis of yellow fever is that of J Austin Kerr in Strode (Ref 29 pp 381 ff) In this article the findings of various clinical laboratory tests are also summarized.

5 HIRSCH August Handbook of geographical and historical pathology 1 316 chap viii "Yellow Fever" Translated from the second German edition London New Sydenham Society 1883

This is the great storehouse of information about epidemics of yellow fever which are listed in detail as to time and place It is pointed out that yellow fever rarely occurs as a pandemic and that epidemic outbreaks never happen suddenly a series of isolated cases always precedes them Often the disease remains limited to one quarter of a town The duration of epidemics varies greatly Many other circumstances of outbreaks are discussed Hirsch regards it as shown that yellow fever is communicable, "it is not now a question of whether communication actually takes place but only of how it takes place" Difference of opinion on this point depends not so much upon conflicting facts but rather the significance ascribed to them" There is of course no mention of the mosquito

The article is followed by a lengthy bibliography

6 FINLAY Carlos J The mosquito hypothetically considered as the agent of transmission of yellow fever Translated by Dr Finlay from the Anales de la Academia de ciencias medicas fisicas y naturales de la Habana 18 147 1881 *In* Trabajos selectos del Dr Carlos J Finlay Havana Republica de Cuba, 1912

To Finlay seems to belong the credit for first clearly insisting that the mosquito was the vehicle for transmission of yellow fever[2] "I feel convinced that any theory which attributes the origin and the propagation of yellow fever to atmospheric influences to miasmatic or meteorological conditions to filth or to neglect of general hygienic precautions must be considered as utterly indefensible

I shall not concern myself with the nature or form of the morbific cause of yellow fever beyond postulating the existence of a material transportable substance which may be an amorphous virus a vegetable or animal germ a bacterium etc but at any rate constitutes something tangible which requires to be conveyed from the sick to the healthy before the disease can be propagated" He then enumerated the reasons which made him select the mosquito as the only suitable vector Finlay postulated that the mosquito carried the virus from

[2] The long rambling article by Josiah C Nott (Yellow fever contrasted with bilious fever—reasons for believing it a disease sui generis—its made of propagation—remote cause probable insect or animalcular origin" New Orleans M & S J 4 563 1848) to whom credit is often given for first claiming that yellow fever is transmitted by the mosquito is thus criticized by Ronald Ross (*Memoirs* [London John Murray 1923]) "Speculations of this kind are apt to be much overrated by penmen It is easy for persons to sit in arm-chairs and weave hypotheses many imagined America before Columbus but an ocean had to be traversed between the dream and reality Theorists who do not trouble to verify their own speculations deserve little credit" (p 424)

In the second communication (Walter Reed James Carroll and Aristides Agramonte "The etiology of yellow fever an additional note" J A M A 36:431 1901) the authors tell first of the establishment of an experimental sanitary station (hospital) under full quarantine for the continuation of their studies There are then reported the details of further inoculation experiments from which the following important conclusions are drawn An interval of about 12 days or more after contamination appears necessary before the mosquito is capable of conveying the infection The bite of the mosquito at an earlier period does not appear to convey any immunity Yellow fever can be produced by subcutaneous injection of blood drawn during the first and second days of the disease The incubation period of the experimental infection varied from 41 hours to 5 days and 17 hours Yellow fever is not conveyed by fomites The spread of yellow fever can be most effectively controlled by destroying mos quitoes and protecting susceptible people against mosquito bite Thus the principal facts of the mode of transmission of yellow fever were definitely estab lished In a third note Walter Reed James Carroll and A Agramonte "Experi mental yellow fever" Am Med 2:15 1901) they describe the clinical features of the experimental disease and emphasize the occurrence of mild cases which can be diagnosed only with difficulty Another paper (Walter Reed and James Carroll "The prevention of yellow fever" M Rec 60:641 1901) soon followed in which the harmful mosquito is described with its habits of breeding and feeding, and a review is given of preventive measures including quarantine which they found requires a longer period than the usual 5 days Meanwhile Reed gave an interesting review of all his work (Walter Reed "The propagation of yellow fever observations based on recent researches" *ibid* p 201) before the Medical and Chirurgical Faculty of the State of Mary land Finally in the last of Reed s early series of papers (Walter Reed and James Carroll "The etiology of yellow fever a supplemental note" Am Med 3 301 1902) he reports the production of yellow fever with serum which has been passed through "a new Berkefeld laboratory filter" He discusses the pos sibility of filtrable toxin but concluded that the agent is probably a filtrable virus

10 REED Walter Recent researches concerning the etiology propagation and prevention of yellow fever by the United States Army commission J Hyg 2 101 1902

The fruits of the commission s studies were not only an understanding of the transmission of yellow fever but invaluable clues to the control of the disease In this lecture Reed after reviewing material already presented in his previous papers tells how under the efficient management of General Gorgas yellow fever was practically extirpated in Havana in one year In October 1900 for example the epidemic reached a peak of over three hundred cases in the same month a year later there were only three cases This amazing result was achieved by quarantine screening and mosquito destruction and set the prece dent for the final elimination of the disease in civilized communities as epi demic after epidemic was stamped out and endemic foci were cleared Gorgas himself (William C Gorgas "Sanitation of the tropics with special reference to malaria and yellow fever J A M A 52 1075 1909) summarized his methods and accomplishments

fortunately took this report as a personal affront and in another paper struck back (G Sanarelli, Some observations and controversial remarks on the specific cause of yellow fever" M News 75 193 1899) angrily but feebly To this Reed and Carroll replied once more ("The specific cause of yellow fever a reply to Dr Sanarelli" M News 75 321 1899) "We pass by therefore as unworthy of comment Sanarelli s insinuation that we could lend ourselves to the support of any personal controversy" They gave many more data and arguments and, finally, in a very comprehensive report (A comparative study of the biological characters and pathogenesis of Bacillus X [Sternberg] Bacillus icteroides [Sanarelli] and the hog-cholera bacillus [Salmon and Smith]" J Exper Med, 5 215 1900) laid the ghost of this controversy

8 CARTER H R A note on the interval between infecting and secondary cases of yellow fever from the records of the yellow fever at Orwood and Taylor Miss in 1898 New Orleans M & S J 52 617 1900

That brilliant if eccentric student of yellow fever H R Carter made the important observation (in a rural community where circumstances were such as to make the induction valid) that after the first case of yellow fever appeared in a certain locale at least 2 weeks elapsed before secondary cases arose Although Carter drew no (written) conclusions as to insect carriage his work helped to strengthen in Walter Reed s mind the probability that the mosquito was the vector of yellow fever (Ref 9)

9 REED Walter CARROLL, James AGRAMONTE A and LAZEAR Jesse W The etiology of yellow fever a preliminary note Philadelphia M J 6 790 1901

The famous yellow fever commission consisting of Walter Reed[3] James Carroll Jesse W Lazear and Aristides Agramonte had recently been assembled at Havana where yellow fever had appeared in American troops This is the first of a series of communications announcing the work of the commission and its conclusions The report deals first with cultures from yellow fever cadavers with more comments on *B icteroides* (see Ref 7) The second part gives a review of Carter s work (Ref 8) "In view of the foregoing observations we concluded to test the theory of Finlay [Ref 6] on human beings" Non immune men were bitten by infected mosquitoes (*Culex fasciatus*) "It will be seen that we record nine negative and two positive results" The two positive cases were bitten by mosquitoes which had fed on yellow fever patients 12 and 10 days previously the "failures" were bitten by mosquitoes which had fed 2–8 days previously The two cases reported in detail are Carroll who survived and Lazear who died

The final conclusion of the paper is this "The mosquito serves as the intermediate host for the parasite of yellow fever and it is highly probable that the disease is only propagated through the bite of this insect"

[3] By far the best and most accurate account of the yellow fever commission and its work is that of Howard A. Kelly *Walter Reed and Yellow Fever* (New York McClure Phillips & Co., 1906) There is a full bibliography of the papers written by the members Other books on Walter Reed dealing to some extent with yellow fever are Albert E Truby *Memoir of Walter Reed* (New York Paul B Hoeber 1943) and L N Wood, *Walter Reed Doctor in Uniform* (New York Julian Messner Inc 1943)

14 NOGUCHI Hideyo Etiology of yellow fever I Symptomatology and pathological findings of the yellow fever present in Guayaquil J Exper Med 29:547 1919

The formation of the Rockefeller Foundation Yellow Fever Commission is told in Strode s book (Ref 29 pp 14 ff) Noguchi was a member of the commis sion and in this paper and its sequels he announced the cause of yellow fever as a leptospira which he named *Leptospira icteroides* This claim of course turned out to be erroneous and Noguchi's apologists have stated that he was actually working on Weil s disease which is easily confused with yellow fever and which is in fact caused by a leptospira A careful scrutiny of the original articles however throws doubt on this position In the present paper for example Noguchi describes at length the disease upon which he worked in the Yellow Fever Hospital at Guayaquil he points out the skill and experience of the personnel and he lays special stress on the accuracy of the diagnosis In the second paper ("II Transmission experiments on yellow fever" *ibid.* p 565) he tells how he injected blood from yellow fever patients into many vari eties of animals and thought that he had produced a disease analogous to yellow fever in guinea pigs "In the blood liver and kidneys of guinea pigs experi mentally infected with the blood of yellow fever patients a minute organism was demonstrated The leptospira obtained from cases of yellow fever has been given the provisional name of Leptospira icteroides" In the next paper ("III Symptomatology and pathological findings in animals experimentally in fected" *ibid.* p 585) the experimental disease produced in guinea pigs dogs and marmosets by injection of infected material or of pure cultures of the organism is described but we are not yet told how the pure cultures were ob tained There follow numerous other papers in which the whole subject be comes more and more confused In Paper VI ("Cultivation morphology viru lence and biological properties of Leptospira icteroides" *ibid* 30 13 1919) isolation of the organism by special culture methods from three of eleven yellow fever patients is reported and its properties are described As he found that it passed through Berkefeld filters Noguchi raised the question of its hav ing a granular phase under certain conditions Examination of fresh blood from yellow fever patients by the dark field microscope made in more than 27 cases revealed the presence of *L icteroides* in three ("VII Demonstration of Lepto spira icteroides in the blood tissues and urine of yellow fever patients and of animals experimentally infected with the organism" *ibid* p 87) Finally in another paper ("IX Mosquitoes in relation to yellow fever" *ibid* p 401) No guchi concluded "The foregoing experiments show that symptoms and lesions *closely resembling those of yellow fever in man may be induced in guinea pigs* by the bite of female Stegomyias that have previously sucked the blood of a yellow fever patient" Within the next few years more papers by Noguchi ap peared, and others also claimed to confirm his work, until Beeuwkes Stokes and Bauer and their associates working on yellow fever in West Africa com pletely failed to isolate *Leptospira* from their cases or to reproduce the disease in small animals (Ref 15) There is an excellent critical review of Noguchi s work in Klotz s De Lamar Lecture (Oscar Klotz *Yellow Fever in West Africa* [Baltimore Williams & Wilkins Co 1928])

A recent authoritative book on all aspects of mosquito control is that of William Brodbeck Herms and Harold Farnsworth Gray *Mosquito Control* (2d ed New York Commonwealth Foundation 1944)

11 THOMAS H Wolferston Yellow fever in the chimpanzee Brit M J, 1 138 1907

There was a general belief that man was the only intermediate host of yellow fever, in other words the cycle was thought to be mosquito–man–mosquito Thomas was the first to report the infection of a monkey by mosquito bite A large number of mosquitoes were fed on a yellow fever patient, and 21 days later the survivors were allowed to bite a chimpanzee who, 27 hours later developed fever and ran the clinical course of yellow fever This experiment anticipated the classical studies of Stokes Bauer and Hudson (Ref 15) and also raised the important question of whether animals aside from man could be storehouses of yellow fever virus in nature (Ref 13) The whole question of various mammalian hosts of yellow fever is discussed in Strode (Ref 29, pp 303 ff)

12 DA ROCHA LIMA H Zur pathologischen Anatomie des Gelbfiebers Verhandl d deutsch path. Gesellsch 15 163 1912

Da Rocha Lima was one of the first to devote a paper exclusively to the anatomical changes of yellow fever However as early as 1890 W T Councilman at the instigation of Sternberg made a report on the histology of yellow fever with special emphasis on the liver changes (see George M Sternberg *Report on the Etiology and Prevention of Yellow Fever* [Washington Government Printing Office 1890] p 151) E Marchoux and P L Simond ("Études sur la fièvre jaune Ann Inst Pasteur 20 161 1906) among their elaborate studies of yellow fever have a section on the pathology of the disease with numerous colored plates The early studies of Louis (Ref 2) are also not to be forgotten For a recent critical discussion of the lesions with a bibliography see Strode (Ref 29 pp 141 ff)

13 BALFOUR Andrew The wild monkey as a reservoir for the virus of yellow fever Lancet 1 1176 1914

Balfour raised the question of whether wild monkeys might not act in some places as a reservoir of yellow fever on the basis of a story that in a certain part of Trinidad red howler monkeys are said to be found dead and dying in the forest preceding an epidemic of yellow fever Certain people who went into the woods also acquired yellow fever Various outbreaks of yellow fever such as that reported by F L Soper H Penna E Cardoso J Serafim Jr M Frobisher Jr and J Pinheiro ("Yellow fever without Aedes aegypti study of a rural epidemic in the Valle do Chandan Espirito Santo Brazil 1932" Am J Hyg 18 555 1933) were obviously not caused by the bite of *Aedes aegypti* and did not occur on the basis of the classical man–mosquito–man cycle Studies of this sort led to the concept of jungle yellow fever with a forest or animal–mosquito cycle propagated in remote areas into which man steps only secondarily It is only in such areas that yellow fever is today endemic. The problem of jungle fever and localities in which foci persist is discussed in detail in Strode (Ref 29 pp 463 ff)

showed that there was no cross immunity between yellow fever and leptospiral jaundice

18 COWDRY F C and KITCHEN S F Intranuclear inclusions in yellow fever Am J Hyg 11:227 1930

The discovery of intranuclear inclusion bodies of a sort common in diseases due to filtrable viruses was of the greatest importance in the etiologic study of yellow fever Such bodies were early described by C M Torres ("Inclusions nucléaires acidophiles [dégénérescence oxychromatique] dans la foie de Macacus rhesus inoculé avec le virus brésilien de fièvre jaune" Compt rend Soc de biol 99 1344 1928) and by Cowdry and Kitchen ("Intranuclear inclusions in yellow fever" Science 69:252 1929) but the present impressive study is definitive The inclusions are described in great detail and are illustrated by beautiful plates They were found both in liver cells of infected monkeys and in human material and are regarded as specific No signs of any such bodies were found in infected mosquitoes "In conclusion the nuclear response in yellow fever is of the same general type which occurs in many other virus diseases especially chickenpox herpes virus III disease and submaxillary disease"

19 BAUER Johannes H and MAHAFFY Alexander F Studies on the filtrability of yellow fever virus Am J Hyg 12:175 1930

Although Stokes Bauer and Hudson (Ref 15) had reported preliminary experiments on the filtrability of yellow fever virus their work was incomplete and Bauer and Mahaffy studied the subject systematically They found that the virus passed through filters without marked diminution in potency serum was infective at times in amounts as small as 0 0000001 cc the lack of infectivity of a filtrate of mosquitoes ground in salt solution was due to the toxicity of the diluent for the virus no evidence was found to indicate that virus in blood differed from that in mosquitoes

20 THEILER Max Studies on the action of yellow fever virus in mice Ann Trop Med 24 249 1930

Although transmission of yellow fever to monkeys was a discovery of the greatest importance monkeys turned out to be difficult to work with and too costly for extensive use A smaller animal was necessary Theiler therefore made a great contribution when he found that yellow fever virus could be established in white mice It occurred to Theiler to try the intrathecal route following injection the animals became sick and at autopsy sections of brain invariably showed an encephalitis and specific nuclear changes Theiler was able to pass the disease indefinitely through mice in this fashion Infective mouse brain stored at −8 C retained its virulence for at least 160 days He was not able to protect mice successfully by an injection of an immune serum The mouse virus produced yellow fever in monkeys Many other details are discussed

21 BERRY G P and KITCHEN S F Yellow fever accidentally contracted in the laboratory a study of seven cases Am J Trop Med 11:365 1931

15 STOKES Adrian BAUER J H and HUDSON N Paul The transmission of yellow fever to Macacus rhesus preliminary note, J A M A 90 253 1928

The authors working under the West African Yellow Fever Commission of the Rockefeller Foundation opened the modern era of yellow fever research by showing beyond question that the disease could be regularly transmitted to *M rhesus* monkeys both by injections of blood from patients and by the bite of infected mosquitoes The disease could also be passed from monkey to monkey both by blood and by mosquito bite Mosquitoes were infective 16 days after feeding on an infected animal and remained so until death Stokes unhappily acquired yellow fever and died before this paper was published

There shortly appeared by the same authors a full report of their work (Experimental transmission of yellow fever to laboratory animals " Am J Trop Med 8 103 1928) They showed in addition that serum passed through Berkefeld and Seitz filters was infective although a filtrate of infected mosquitoes macerated in salt solution failed to produce disease The specific pathological findings in infected monkeys are reported in detail They also showed that convalescent serum in doses of 0 1 cc protected monkeys against infection while 2 cc of normal human serum failed to protect Numerous other phases of the subject are discussed

The circumstances of this epoch making work are graphically told by Wilbur A Sawyer "Recent progress in yellow fever research Medicine 10 509 1931

Stokes Bauer and Hudson s work was soon confirmed by C Mathis A W Sellards and J Laigret (Sensibilité du Macacus rhesus au virus de la fièvre jaune Compt rend Acad d sc 186 604 1928) who isolated in monkeys at Dakar the famous "French" strain which was much used in later experimental work

16 BAUER Johannes H The transmission of yellow fever by mosquitoes other than Aedes aegypti Am J Trop Med 8 261 1928

It had heretofore been thought that *Aedes aegypti* was the only mosquito which could transmit yellow fever Bauer found in West Africa that A luteocephalus and A africoannulatus transmitted this disease in all respects in the same manner as A aegypti thus opening the subject of multiple vectors A full discussion of the complicated question of arthropod vectors of yellow fever is given in Strode (Ref 29 pp 233 ff)

17 SAWYER W A KITCHEN S F FROBISHER Martin Jr and LLOYD Wray The relationship of yellow fever of the Western Hemisphere to that of Africa and to leptospiral jaundice J Exper Med 51 493 1930

There had been great uncertainty whether "yellow fever in various localities was the same disease In South America for example Noguchi had isolated a leptospira (Ref 14) which was not obtainable in West Africa by Stokes and his associates Sawyer and his associates collected strains of virus from all over the world and by cross protection tests showed that the yellow fever now in South America the present yellow fever of Africa and the historic yellow fever of Panama and other American countries are the same disease " They also

The writers were the first successfully to cultivate yellow fever virus in the developing chick embryo John P Fox and Hugo W Laennert Jr ("The cultivation of yellow fever virus II Observations on the infection of developing chick embryos" Am J Hyg 46:21 1947) elaborated these observations With reference to human vaccination they showed that prolonged passage of the 17 D strain did not apparently alter the virus and did not increase neurotropic virulence for monkeys or man

26 WHITMAN Loring The multiplication of the virus of yellow fever in Aedes aegypti J Exper Med 66:133 1937

After reviewing some older and inconclusive work, the authors showed that following an incubation period titers of virus can be recovered from mosquitoes which are significantly higher than at any preceding time" They concluded that "Aedes aegypti have been shown to be capable of multiplying the Asibi strain of yellow fever virus in their bodies Following the ingestion of infected blood the content of virus falls for several days reaching a minimum during the first week It then increases rapidly until quantities of virus greater than those previously encountered can be demonstrated" At about the same time L. Whitman and P C. A Antunes (Studies on Aedes aegypti infected in the larval stage with the virus of yellow fever" Proc Soc Exper Biol & Med 37 664 1938) showed that "Aedes aegypti can be infected in the larval stage with the virus of yellow fever providing they are exposed to large quantities of virus The resultant adults both male and female are infected"

27 THEILER Max and SMITH Hugh H The use of yellow fever virus modified by in vitro cultivation for human immunization J Exper Med 65 787 1937

Using a strain of yellow fever virus modified by prolonged cultivation the authors vaccinated human beings without the simultaneous injection of immune serum Eight normal persons were used with minimal reactions and their sera 2–4 weeks after inoculation showed the presence of yellow fever antibodies H H Smith H A Penna and A Paoliella ("Yellow fever vaccination with cultured virus [17 D] without immune serum" Am J Trop Med 18 437 1938) grew the virus in chick embryos and prepared a vaccine which they used on a large scale with good results G M Findlay and F O MacCallum ("Note on acute hepatitis and yellow fever immunization Tr Roy Soc Trop Med & Hyg 31 297 1937) were the first to report a considerable number of instances of acute hepatitis following yellow fever vaccine they came to no definite conclusions as to cause With the occurrence of many cases of acute hepatitis following mass vaccination in the United States Army W A Sawyer K F Meyer M D Eaton J H Bauer Persis Putnam and F F Schwentker ("Jaundice in army personnel in the western region of the United States and its relation to vaccination against yellow fever" Am J Hyg 39 337 1944 40 35 1945) took up the subject in earnest and issued a report on their elaborate studies "The most plausible hypothesis as to the source and nature of the icterogenic agent was that it had been introduced into the vaccine in human blood serum secured from supposedly normal donors and used in manufacture of the vaccine that the agent was most probably an unknown filtrable virus capable of causing disease in man"

In the course of their meticulous studies on 'laboratory' yellow fever Berry and Kitchen, after reviewing the previous literature report careful counts of the leukocytes They noted a progressive fall in number from onset to the fifth or sixth day The counts fell as low as 2 625 the polymorphonuclear neutrophils dropping to levels as low as 500–1 000 From the sixth to eighth days the total leukocyte count increased soon reaching normal levels

22 SAWYER W A and LLOYD Wray The use of mice in tests of immunity against yellow fever, J Exper Med 54 533 1931

The need of a test for immunity to yellow fever had become obvious Following Theiler, Sawyer and Lloyd developed a workable and reliable protection test in mice The unknown serum to be tested for its protective power was mixed with yellow fever virus fixed for mice and injected intraperitoneally into mice which had been prepared by an intracerebral injection of starch solution If the serum was protective the mice remained well if not the virus localized in the brain at the site of the starch injection This test has turned out to be of great value both in research and in epidemiological studies

23 SAWYER, W A KITCHEN S F and LLOYD Wray Vaccination against yellow fever with immune serum and virus fixed for mice J Exper Med 55 945 1932

"The method here presented for vaccination against yellow fever was devised primarily to interrupt the long series of accidental infections of persons making laboratory investigations" The writers first review previous unsatisfactory attempts at vaccination and then describe their own method After preliminary experiments on monkeys 15 persons were actively immunized by a single injection of a dried mixture of living yellow fever virus fixed for mice and human immune serum with separate injections of enough additional serum to make up the amount required for protection Immunity rose in a few weeks to a height comparable to that reached after an attack of yellow fever and remained there through an observation period of 2 months"

24 LLOYD Wray THEILER Max and RICCI N J Modification of the virulence of yellow fever virus by cultivation in tissues *in vitro* Tr Roy Soc Trop Med & Hyg 29 481 1936

Although E Haagen and M Theiler ("Untersuchungen uber das Verhalten des Gelbfiebervirus in der Gewebecultur" Centralbl f Bakt 125 145 1932) had successfully grown a neurotropic strain of yellow fever virus in a medium of minced chicken embryo tissue and serum Tyrode solution no one had succeeded in growing an unmodified pantropic strain This the authors succeeded in doing during a period of 21 months and through more than 150 subcultures The complicated technique is described as well as various antigenic characteristics of the virus and the immunological reactions A little later Hugh H Smith and Max Theiler ("The adaptation of unmodified strains of yellow fever virus to cultivation *in vitro*" J Exper Med 65 801 1937) succeeded in cultivating yellow fever virus in a medium containing mouse embryo brain tissue

25 ELMENDORF John E Jr and SMITH Hugh H Multiplication of yellow fever virus in the developing chick embryo Proc Soc Exper Biol & Med. 36 171 1937

HERPES ZOSTER

Clinical	Refs 2 6
Demonstration of virus	Ref 14
Generalized herpes	Ref 9
Herpes encephalitis	Refs 7 15
Herpes following trauma	Refs 1 2 6
Herpes and varicella	Refs 11 12 14
Historical	Ref 2
Inclusion bodies	Ref 10
Infectious nature	Ref 5
Ophthalmic herpes	Ref 4
Otitic herpes	Ref 8
Pathology	Refs 3 6
Relation to C N S	Refs 2 6
Transmission to animals	Refs 10 13
Transmission to man	Ref 12

The whole story of induced immunity to yellow fever is told in Strode (Ref 29 pp 203 ff)

28 PICKELS, Edward G and BAUER Johannes H Ultrafiltration studies of yellow fever virus J Exper Med. 71 703 1940

The writers already knew the approximate size of the virus particles from observations made in previous ultrafiltration studies (J H Bauer and T P Hughes Ultrafiltration studies with yellow fever virus" Am J Hyg 21 101 1935) In the present study they observed in the ultracentrifuge by optical methods the behavior of yellow fever virus particles directly in the unaltered serum from infected monkeys and were able to estimate the size of the particles to be between 12 and 19 mμ For a detailed discussion of the physical and chemical properties of the virus see Strode (Ref 29 pp 46 ff)

29 STRODE George K (ed) Yellow fever New York McGraw Hill Book Co 1951

An impressive compilation dealing with all phases of yellow fever, with a comprehensive bibliography An invaluable reference book

of scabs red scars remain which later become pale and usually leave no trace" In most cases the disorder is painless except for slight burning But sometimes the patients complain of severe burning which they liken to red hoat coals it increases with warmth prevents sleep and the slightest touch causes pain" Von Barensprung remarks that the pain may be severe with a very small area of eruption and in other cases the pain spreads not only through the affected area but through "neighboring nerve domains Pain often precedes the eruption by a shorter or longer time and remains with great severity long after healing As to etiology "Zoster is an inflammation of the skin of typical form and course the essential peculiarity of which is that it appears to be confined to the peripheral domain of cerebral and spinal nerves or their branches The eruption has a noteworthy correspondence with the distribution of the nerves of the skin these facts justify the conclusion that the cause of the inflammation is not carried in from the surface or by way of the blood but rather through the nerves themselves" The distribution of the eruption rules out a central source By exclusion he finally settled on the posterior nerve roots as the source of the disease or more specifically the posterior root ganglia in which he thought that sympathetic fibers coursed Of the exact nature of the irritation of the ganglia and nerves which led to zoster Von Barensprung had no idea Treatment stood much the same as today there was no effective remedy but he emphasized the importance of protecting and not interfering with the vesicles

This monograph is a model of good organization accurate description and keen reasoning with few exceptions what is said stands today Von Barensprung's paper excited great interest in the subject, and descriptions of cases seen by others and reported to him are detailed in another paper ("Fernere Beitrage zur Kentniss des Zoster" *ibid* 10 37 1862)

3 VON BARENSPRUNG Beitrage zur Kenntniss des Zoster (Dritte Folge) Ann. d Charité Krankenhaus 11:96 1863

Von Barensprung reiterated his views that the posterior root ganglia were the site of the initial trouble in herpes zoster He went wrong however in thinking that the ganglia had a system of special nerve fibers of their own which had no connection with the fibers of the posterior root and of the peripheral nerve An autopsy on a baby with herpes who died of pulmonary tuberculosis confirmed Von Barensprung's ideas about the site of the disease "One was struck by the increased thickness and redness of the sixth, seventh and eighth nerves especially the seventh which seemed to depend on swelling with dilated and tortuous vessels running through the neurilemma The spinal ganglia belonging to these three nerves were adherent to the wall of the intervertebral canal the connective tissue here also was reddened and thickened so that the volume of the ganglion seemed increased The microscope also disclosed indubitable residuals of inflammation The autopsy showed then what we expected in advance that in zoster one was not concerned with a destructive process but with a mild reversible change It seems of special interest that the inflammation of the ganglion does not extend along the posterior root to the cord but only in the peripheral direction Thus he thought the findings indicated an inflammation in the substance of the ganglion and not just in the neurilemma While his interpretation was not altogether correct he deserves credit for first clearly stating the relation of the eruption to the spinal ganglia

Section 29

HERPES ZOSTER

MUCH of the bibliography of herpes zoster is concerned with the relation of the disease to other vesicular dermatoses especially chickenpox This puzzling question is not yet entirely settled although it appears from the literature that there must be a close relation between if not an identity of the causal agents Thorough modern discussions of the whole problem of chicken pox and zoster with bibliography are to be found in the recent book by Harvey Blank and Geoffrey Rake *Viral and Rickettsial Diseases of the Skin Eye and Mucous Membranes of Man* (Boston Little Brown & Co 1955) (p 71) and in the article by J Stokes "Varicella-herpes zoster group" in T M Rivers (ed), *Viral and Rickettsial Infections of Man* (2d ed Philadelphia J B Lippincott Co 1952) (p 506) R Doerr s review (Ergebnisse der neueren experimentellen Forschungen uber die Atiologie des Herpes simplex und des Zoster Zentralbl f Haut u Geschlechtskr 15 1 1924) covers the experimental side to date whereas the monumental review by W Schonfeld ("Zoster," in *Handbuch der Haut und Geschlechtskrankheiten* [1928] Vol 7, Part I) reviews the entire literature to 1928 including a section on the history of the disease

1 CHARCOT Note sur quelques cas d affection de la peau dépendent d une influence du système nerveux Obs III Névralgie consecutive à une lésion traumatique et accompagnée d une éruption de vésicules d'herpes *J de physiol de l'homme et des animaux* 2 111 1859

There is a huge literature on "secondary" herpes herpes following the use of certain drugs such as arsenic following fevers with lymphatic leukemia with malignancy of various sorts and following trauma Charcot reports an early case after an injury There has been in the modern literature which is reviewed by J Klauder ("Herpes zoster appearing after trauma" J A M A 134 245 1947) much dispute as to the relation of trauma to viral infection in certain cases of zoster

2 VON BARENSPRUNG [Felix] Die Gurtelkrankheit Ann d Charité Krankenhaus 9 40 1861

The modern study of herpes zoster may be said to begin with this classical paper or rather monograph since it occupies ninety pages After a historical introduction and an account of the origin of the term "herpes Von Barensprung gives a systematic discussion of the topography of the lesions based on cases he had actually observed From the beginning of my medical studies I have noted all cases which I have seen and have sketched many of them" He insists on the unilateral occurrence of the eruption and gives detailed case reports with graphic sketches of the areas involved These are followed by a clinical analysis Fever was noted in only 5 of 65 cases The eruption is described as a sequence of erythema papule and vesicle "The slightly alkaline content of the vesicles is a light serum without solids later it becomes milky as the white cellular layer becomes emulsified in it very rarely it becomes purulent Scab formation between the fifth and eighth days after the separation

the severity of the acute destruction The anterior root was in all cases normal" There were also degenerative changes in the fibers that entered the posterior root ganglia as well as acute degeneration in the posterior columns of the spinal cord These lesions are all beautifully pictured in colored drawings microphotographs and diagrams Special sections are devoted to zoster of the trigeminal nerve zoster secondary to implication of the ganglion in general disease processes and zoster arising in the course of diseases of the nervous system As to changes in the skin "Sections through an unruptured vesicle of herpes zoster show a cavity the floor of which is formed of naked papillae These papillae are in a condition of profound inflammation and are infiltrated with masses of small round cells which stain deeply The vesicle is split into incomplete cavities by septa extending from the roof to the floor These septa are evidently the remains of incompletely raised epithelial layers that retain their attachment to the roof and to the floor of the vesicle microscopic examination of the fluid and careful staining of the sections of the skin failed to reveal any sign of micro-organisms The lymphatic glands enlarge and frequently become tender very early in the disease" Head and Campbell regarded zoster as an acute specific disease analogous to lobar pneumonia They commented on its occurrence at times in epidemics the rarity of second attacks and the analogy to anterior poliomyelitis "Of the nature of the agent which is responsible for this process we are completely ignorant Microscopically we have not been able to find any signs of bacterial infection The unknown agent responsible for the inflammation in the ganglion not only shows a specific attraction for the posterior root ganglia but commonly attacks one ganglion only This selection of one group of cells is also partly characteristic of the poison that causes anterior poliomyelitis

But if the case be seen before the rash appears it is sometimes possible to map out the area subsequently occupied by the eruption by means of the hyperalgesia that is present This hyperalgesia is followed by erythema Then on the erythematous surface vesicles appear"

The remainder of the study consists of meticulous comparisons of the skin areas involved with the lesions in the dorsal roots at autopsy On the basis of these observations were mapped the classical "Head s zones" which are illustrated by detailed diagrams

7 CHAUFFARD A and FROIN G Nature évolution et durée de la réaction méningée dans la zona Bull et mém Soc méd d hôp de Paris 19 994 1902

Although changes in the spinal fluid in herpes zoster had been noted before Chauffard and Froin seem to have been the first to recognize them as indicative of an encephalitis One must admit that there is a toxi infectious impregnation of the entire neuraxis when one sees an ophthalmic zona accompanied by such an intense lymphocytosis in the spinal fluid it is quite comparable in its morphology to that which gives rise to the most characteristic spinal infectious processes such as tuberculous meningitis tabes or general paralysis" Later C I Schiff and W Russell Brain ("Acute meningo-encephalitis associated with herpes zoster" Lancet 2 70 1930) reviewed the literature and reported a fatal case of their own He not only died of acute meningoencephalitis but showed aberrant herpes vesicles and apparently transmitted varicella to his son

4 HUTCHINSON Jonathan. A clinical report on herpes zoster frontalis seu ophthalmicus (shingles affecting the forehead and nose) Ophthal Hosp Rep 5 191 1866

Hutchinson refers to a few previous isolated case reports, but he was the first to deal systematically with the subject. The disease is thought to be rare and is probably often misdiagnosed erysipelas "Herpes frontalis is always limited to one side, never transgresses the median line of the forehead and nose It never affects the cheek, although there may be some sympathetic edema of the part. There can be little doubt that the local processes of inflammation in the skin and eyes are produced directly through the medium of the nerves in this instance of the ophthalmic division of the fifth" There are eighteen detailed case reports

5 [LANDOUZY] Fievre zoster et exanthemes zosteriformes (leçon recueillie par M le docteur H Jonas chef de clinique) Semaine méd. 3 245 1883

Landouzy seems to have been the first to insist in emphatic terms on the infectious nature of zoster Aside from fever and occurrence in epidemics he stressed the fact that only infectious diseases confer immunity against further attacks He concludes "(*a*) zoster is an acute disease almost cyclic infectious conferring immunity a generalized disease an infectious neuropathy with secondary cutaneous dystrophy (*b*) zoster is a generalized disease like scarlatina. There is a zoster fever as there is a scarlatinal fever, zosteriform eruptions as there are scarlatiniform exanthems"

6 HEAD Henry and CAMPBELL, A. W The pathology of herpes zoster and its bearing on sensory localization Brain, 23 353 1900

This is the classical article in which, on the basis of herpetic eruptions the peripheral distribution of the sensory roots was worked out by Head and Campbell the diagrams here first published are the ones familiar to every student in his textbooks for the next fifty years Head and Campbell first review the literature on the pathology of zoster and point out that since Von Bärensprung (Ref 3) there had been only five adequately reported autopsies To these Head and Campbell added twenty-one

Next is a general discussion of the pathology of zoster It is pointed out that, at the height of the eruption, "the affected ganglion will be found to be in a condition of profound inflammation The interstitial tissue will be crowded with small round cells which stain deeply with methylene blue and other nuclear dyes If these foci of inflammatory cells are examined in several sections they will occasionally be found to be situated around extravasated blood. In the centre of these haemorrhagic foci the ganglion cells are absolutely destroyed ultimately the focus of inflammation becomes converted into fibrous tissue and the density and extent of this scar depend on the severity and extent of the original inflammation." Corresponding to the affection of the ganglia Head and Campbell demonstrated degeneration in the posterior roots "and it is probable that this degeneration begins to make its appearance ten days after the appearance of the eruption" The changes consisted of "an acute degeneration followed by a greater or less amount of secondary sclerosis according to

42:709 1925) critically analyze the literature pro and con on transmission of herpes to animals and come up with a verdict of "not proved Their own carefully performed experiments in which they repeated Lipschutz inoculation of the rabbit s cornea all turned out negative Nor were they able to produce evidence of herpes in monkeys Direct inoculation into the central nervous system was negative and so was intra testicular inoculation of rabbits S Seidenberg (Untersuchungen uber das Herpes und Zostervirus" Ztschr f Hyg u Infectionskr **112**:134 1931) using modern techniques was also unable to produce a reaction in the rabbit s cornea with material from zoster vesicles although corneas treated in this way did not become immune to inoculation with herpes simplex material W J Cheatham ("The relation of heretofore unreported lesions to pathogenesis of herpes zoster" Am J Path **29** 401 1953) later described inclusion bodies in the dorsal root ganglia and elsewhere scattered widely through the body

11 V BÓKAY Johann Ueber die Herpes zoster Varizellen Frage Jahrb f Kinderh **105**:8 1924

Von Bókay tells how in 1888 he saw a child who had typical herpes zoster and 10 days later another child in the family developed chickenpox Soon after he saw a similar sequence of events in another family These observations so strongly suggested a relation between chickenpox and herpes that in a paper written in 1909 (J V Bókay "Ueber den atiologischen Zusammenhang der Varizellen mit gewisser Fallen von Herpes zoster" Wien klin Wchnschr **22** 1323 1909) he said "Varicella virus as a result of unknown circumstances can call forth, instead of a general eruption a typical zoster and from the zoster varicella is transferred to other individuals" Suggestive observations by others are also reviewed He added (1924) "Naturally I invoked the varicella etiology only in a portion of the zoster cases" He later saw varicella occur in a patient with zoster and now (1924) he analyzed the whole literature in a somewhat nostalgic way and reported further relationships He concluded "I described the fundamentals of the clinical picture of Herpes zoster varicellosis 35 years ago at the beginning of my career and I feel happy now in old age that in the course of time the disease picture built up by me has been accepted by the specialists at home and abroad Furthermore our previous concepts of zoster have not been altered by the Zoster varicellosis described by me since it has of course been known for a long time that zoster does not comprise an etiologically uniform disease" Von Bókay s thesis received support by Bruusgaard s inoculation experiments (Ref 12) and by the work of E Paschen (2 Elmentarkorperchen im Blascheninhalt bei Herpes zoster und Varizellen Centralbl f Bakt **130** 190 1933) who demonstrated in the vesicle fluid of zoster elementary bodies similar in appearance to those found in varicella Paschen s observations were confirmed by C R Amies ("The elementary bodies of zoster and the serological relationship to those of varicella Brit J Exper Path **15** 314 1934) who showed that pure suspensions of these bodies prepared by high speed centrifugalization of zoster vesicle fluid are specifically agglutinated by zoster convalescent sera and that attempts to demonstrate the relationship of zoster and varicella by means of cross agglutination tests have met with a fair measure of success The final link is perhaps forged by

8 HUNT J Ramsay On herpetic inflammations of the geniculate ganglion a new syndrome and its complications J Nerv & Ment Dis 34 73 1907

P Strübing (Herpes zoster und Lahmungen motorischer Nerven " Deutsches Arch f klin Med 37 513 1885) reviews the older literature and reports a case in which herpes was associated with facial paralysis O Korner (Ueber den Herpes zoster oticus [Herpes an der Ohrmuschel mit Lahmung des Nervus acusticus und des Nervus facialis] " Munchen med Wchnschr 51:6 1904) carried the subject further but Hunt is generally recognized as having written definitively insofar as he related the cases to lesions of the geniculate ganglion He divided the clinical syndrome into three groups "(1) Herpes zoster auricularis (2) Herpes zoster in any of the zoster zones of the cephalic extremity (herpes auricularis herpes facialis and herpes occipito-collaris) with facial palsy (3) Herpes zoster of the cephalic extremity with facial palsy and auditory symptoms (tinnitus deafness vertigo vomiting nystagmus and disturbances of equilibrium)

9 WEBER F Parkes Two cases of herpes zoster associated with a generalized eruption of varicella like spots one of the cases followed by oculomotor paresis mydriasis and frontal anesthesia Brit J Dermat 28 13 1916

Parkes Weber that master of the reporting of rare cases discusses the whole subject of generalized vesicular eruptions with herpes zoster with a thorough review of the literature It appears that the question of generalized eruptions as a modified form of varicella did not arise until after Von Bókays paper (Ref 11) At any rate leukemia seems to predispose both to local herpes and to generalized eruptions

10 LIPSCHÜTZ B Untersuchungen uber die Aetiologie der Krankheiten der Herpesgruppe (Herpes zoster Herpes genitalis Herpes febrilis) Arch f Dermat u Syph 136 428 1921

Lipschutz seems to have been the first to demonstrate by special stains inclusion bodies in the cells at the site of the eruption of herpes He concluded that these bodies were derived from "autochthonous nuclear substance" and were the expression of a specific cellular or nuclear reaction to the virus of herpes zoster He thus definitely departed from previous views that such bodies were parasites He inclined to a filtrable virus as the cause and quoted Rist as saying as long ago as 1904 Perhaps we are concerned with one of those microbes called invisible which have been demonstrated in molluscum contagiosum etc "[1] In four of seven attempts he produced a keratitis in the rabbit cornea with material from herpes zoster with characteristic inclusion bodies He later stated that herpes zoster could be transmitted only "occasionally" in contrast to herpes genitalis and herpes labialis which would "take" on the rabbit cornea in approximately 100 per cent of the cases Lipschutz felt that he had demonstrated that the "infection was not only in the central nervous system but in the skin lesions which many had thought were "trophic" in nature R Cole and A. Kuttner ("The problem of the etiology of herpes zoster " J Exper Med ,

[1] E Rist in article "Zona" in E Besnier L. Brocq and L. Jacquet *La Pratique dermatologique* (Paris Masson et Cie 1904) 4:920

1948) They used human prepuce as a source of epidermis and added penicillin and streptomycin to obviate most bacterial contaminations Chicken embryo tissues themselves seemed non susceptible

14 RAKE G BLANK H CORIELL L L NAGLER F P O and SCOTT T F McN The relationship of varicella and herpes zoster electron microscope studies J Bact 56 293 1948

In zoster vesicle fluid collected 24–144 hours after the first appearance of the vesicle the authors found it hard to demonstrate viral bodies by means of the electron microscope However in a specimen withdrawn only 12 hours after the appearance of the vesicles elementary bodies were plentiful although 48 hours later most of the particles had disappeared The bodies closely resembled those previously described by F P O Nagler and G Rake ("The use of the electron microscope in diagnosis of variola vaccinia and varicella" J Bact 55 45 1948) in varicella Average measurement was 196 by 218 mμ about 8 per cent smaller than those seen in chickenpox In another case of zoster fluid was examined that apparently initiated an outbreak of varicella Scanty but characteristic brick shaped bodies were found in both the zoster and the varicella fluids Here then is further evidence of the relationship of zoster and varicella viruses

15 CARTER A Barbeau. Investigation into the effects of aureomycin and chloramphenicol in herpes zoster Brit. M J 1 987 1951

Carter made a systematic study of the spinal fluid in zoster in 44 cases the fluid was abnormal in 14 of which 10 were of the ophthalmic type The protein was as high as 210 mg and the cells as many as 62 soon after the eruption in some cases the fluid was still abnormal after 3 weeks or more These observations were made in the course of a study of antibiotics in zoster which incidentally yielded no beneficial effects However as long ago as 1901 Brissaud and Sicard ("Cytologie du liquide céphalo-rachidien au cours du zona thoracique" Bull et mém Soc méd d hôp de Paris 18 260 1901) found in two cases of zoster an increase in mononuclear cells in the fluid The entire literature to 1928 is reviewed in Schonfeld (*op cit* p 30) All observers agreed that changes in the fluid did not occur in every case of zoster "They are to be looked upon as secondary that is as expressions of the extension of the inflammatory process to surrounding areas (*ibid*)

the similarity in appearance of the viruses of chickenpox and herpes in the electron microscope (Ref 14) H Blank and G Rake (*op cit* p 71) sum the matter up by saying It is believed that there is now sufficient evidence to consider chickenpox (varicella) and zoster (herpes zoster shingles zona) as different clinical manifestations of infections with the same virus However certain discrepancies still exist which are analyzed by J Stokes in his article Varicella-herpes zoster group in Rivers (*op cit* pp 509 ff) It has been pointed out for example that zoster is non contagious whereas varicella is highly communicable that a leukopenia with relative mononucleosis is the rule in chickenpox but not in zoster that both chickenpox and zoster confer immunity against a second attack of the same disease but not against each other Useful epidemiological observations in the relation of the two diseases are given in the report of the School Epidemics Committee *Epidemics in Schools* (Medical Research Council Special Report Series " No 227 [1938]) page 181

12 KUNDRATITZ Karl Experimentelle Ubertragungen von Herpes zoster auf Menschen und die Beziehungen von Herpes zoster zu Varicellen Ztschr f Kinderh 39 379 1925

Kundratitz points out that no one so far has succeeded in transmitting herpes zoster to man He inoculated fluid from herpes vesicles into the arms of children by scarification and concluded 'The inoculation of herpes zoster vesicle fluid from person to person in childhood up to 5 years of age has definitely been successful Thereby the infectiousness of herpes zoster for man and the presence of the virus in the vesicle fluid has been unimpeachably demonstrated Detailed protocols are given At the point of vaccination after about 9 or 10 days small vesicles appeared which had the apperance of chickenpox vesicles Vaccinations of children who had had chickenpox did *not* take He interpreted these findings as in favor of the identity of the viruses of herpes and varicella Kundratitz work was confirmed by E Bruusgaard ('The mutual relation between zoster and varicella " Brit J Dermat 44:1 1932) who succeeded in producing a varicella like eruption in children by vaccination with fluid from herpes vesicles

13 GOODPASTURE Ernest W and ANDERSON Katherine Infection of human skin grafted on the chorioallantois of chick embryos with the virus of herpes zoster Am J Path 20 447 1944

E W Goodpasture B Douglas and K Anderson ("A study of human skin grafted upon the chorioallantois of chick embryos " J Exper Med 68 891 1938) had previously developed a method of transplanting human skin into chick embryos Such transplants were now inoculated with fluid from zoster vesicles and were successfully infected with the virus of herpes zoster The experimental lesions did not vesiculate grossly but became pustular and otherwise remembled those in the natural disease including the presence of intranuclear acidophilic inclusions first described by Lipschutz [Ref 10] in the affected epithelial cells " This work was confirmed by H Blank L L Coriell and T F McN Scott (Human skin grafted upon the chorioallantois of the chick embryo for virus cultivation " Proc Soc Exper Biol & Med 69 341

MUMPS

Clinical	Refs 1 2 4
Complement fixation tests	*Ref 14*
Epidemiology	Refs 2 8 13
Experimental mumps	Refs 7 10 11
General	*Refs 1 2 4*
Immunity	Refs 11 14
Incubation period	Ref 3
Neurological complications	*Refs 1 6*
Orchitis	Ref 5
Pancreatitis	Ref 9
Pathology	*Refs 5 12 21*
Prophylaxis	Refs 15 17
Virus cultivation measurement etc	Refs 16 18 19 21

increasing a swelling appears upon the parts the following day and quickly extends to the parotid glands the neighboring skin and cellular membrane Here in some it stops without discolouring the skin and by keeping the parts moderately warm and cautiously avoiding the cold external air the patient is soon freed from it without any medical assistance But when this is not the case the parts affected generally redden the next day the tumor becomes more diffused and sometimes increases so suddenly in size that on the third day from its first appearance it occupies the salivary glands and surrounding cellular membrane on that side and if both sides are affected the parts are so much swelled and the tumor descends so low that the countenance is rendered of a frightful enormous magnitude and now deglutition becomes more or less impeded All this is frequently without much pain but most commonly there is now a great deal and a considerable degree of fever When this happens the countenance appears florid and a dusky erysipelatous inflammation covers the tumor which is deepest in colour where there is the greatest hardness viz. on the parotid and maxillary glands In many subjects here it ends And it seems probable from the natural resolution of the disease which now immediately follows that the tumor has attained its greatest magnitude and the distemper its acmé for about the morning of the fourth day from the first appearance of the swelling a discharge begins from the emunctories behind the ears a dew like sweat frequently in large drops issues from every pore of the extended surface of the tumor a gentle diaphoresis covers the body if in bed the inflammation abates the swelling gradually lessens and with these favourable circumstances the fever goes off and the distemper totally disappears about the fifth day if nature is not interrupted in her business But if the tumor subsides suddenly about the fourth day and one or both testicles begin to swell sometimes with much pain heat inflammation new rigors and a fresh exacerbation of fever much is to be apprehended from this new morbid appearance and much circumspection is required in the treatment of it For the means employed by nature to promote the resolution of the tumified testes are exactly similar to those which take place in the termination of the tumors below the ears a spontaneous discharge issues from the skin of the parts affected and if this is copious and continued and accompanied with a free perspiration from the surface of the whole body in bed the disease ends happily without farther trouble but if it is scanty partial or interrupted by accidental cold or imprudent treatment the tumors of the testicles subside suddenly the patient becomes restless a fresh exacerbation of fever insues the head is affected delirium follows with convulsions and other dreadful symptoms and sometimes death closes the scene"

Hamilton observed swelling of the testicles followed by atrophy but it is a question whether or not he described true neurological complications "On the day following this the testicles were found lessened in size and the patient was become restless delirious and with much fever He gradually recovered. Another case a man of twenty two is mentioned "The catastrophe was dreadful For the swelled testicles subsided suddenly the next day the patient was seized with a most frantic delirium the nervous system was shattered with strong convulsions and he died raving mad the third day after"

MUMPS

ALTHOUGH mumps is thought of as a relatively insignificant disease it boasts of a surprisingly prolific literature Until the 1930s clinical and epidemiological questions were especially pursued but following the work of Johnson and Goodpasture (Refs 10 11 12) and the development of modern technical methods mumps has served as a topic for endless study along virological lines

As to general accounts and bibliographies, the book of Comby is to be specially mentioned[1] Perhaps the best comprehensive treatise is the one by H Schottmuller *Parotitis epidemica* (Vienna Alfred Holder 1904) which deals with every phase of the disease to date and contains a selected bibliography of 176 titles C Wesselhoeft s discussion ("Mumps its glandular and neurologic manifestations" in J E Gordon *et al* *Virus and Rickettsial Diseases* [Cambridge Mass Harvard University Press 1940] p 309) carries the subject further with a more modern bibliography and John F Enders authoritative article on "Mumps in T M Rivers *Viral and Rickettsial Infections of Man* (2d ed Philadelphia J B Lippincott Co 1952) page 512 brings the subject up to date An excellent chapter on mumps with special emphasis on recent virological and immunological work is to be found in C E Van Rooyen and A J Rhodes *Virus Diseases of Man* (New York Thomas Nelson & Sons 1948)

1 HAMILTON, Robert An account of a distemper by the common people of England vulgarly called the mumps Trans Roy Soc. Edinburgh 2 59 1790

Hamilton is much quoted as early insisting on the contagiousness of the mumps In this account however he makes no direct claim but simply says 'The mumps made its appearance in an epidemic form at Lynn in 1758 Two companies of the Norfolk regiment of militia were quartered here It raged more among these soldiers in proportion to their numbers than amongst the inhabitants of the town" However Hamilton refers to a work by Dr Russel who thinks it contagious" and he also states that people are not liable to have this disease more than once"

Hamilton gives a detailed and brilliant description of the clinical features A lassitude a heaviness a general restless uneasiness not easily described are perceived several days before the swelling which characterises the disease begins to appear These disagreeable feelings are attended with gentle rigors and some degree of fever which being slight is commonly disregarded Then a stiffness with obtuse pain is felt in one or both sides of the articulation of the lower jaw impeding its motion and of course mastication which symptoms

[1] J Comby *Les Oreillons* (Paris 1893) We have been unable to see a copy of this much-quoted book It is not in the Lane Medical Library the copy in the Army Medical Library is unavailable nor is it among the holdings of the New York Academy of Medicine

contagiosité des oreillons " Bull et mém Soc méd d hôp de Paris 10 107 1893) was fortunate enough to observe two patients with mumps whose only exposure to others was in the 48 hours before the onset of clinical symptoms Antony (Oreillons quelques considérations sur leur contagiosité et leur évo lution Bull et mém Soc méd d. hôp de Paris 10: 150 1893) from a study of mumps in an army camp also concluded that the disease was most com municable during the incubation period although it was also "transmissible after healing for an as yet indeterminate period "

4 TROUSSEAU A Clinique médicale de l Hôtel Dieu de Paris 1:218 Mumps (oreillons) " Paris J B Baillière et fils 1861

Trousseau describes the disease in his usual precise and masterful fashion He differentiates mumps from "parotiditis" "They are essentially different affections One is an inflammation of the gland of the cellular tissue which is a component of it and this inflammation which occurs during the course of severe fevers in general, may and does frequently go on to suppuration The other never terminated with suppuration Furthermore while parotiditis generally affects only one side in mumps the two sides are implicated one it is true a little before the other " Thus he clearly differentiated mumps from suppurative parotitis a condition common at the time and often confused with mumps "Mumps are a specific disease with many resemblances to the eruptive fevers Like them specific, like them actively contagious they attack usually the young although they attack at times adults or the aged " Then comes a brief vivid description of the familiar clinical features with a discussion of metastases in men to testes epididymis and tunica vaginalis in females to the breast or sometimes the labia Mumps are then characterized by a swelling of the parotid glands I will add of the salivary glands in general because the submaxillary and sublingual are often affected They manifest themselves by a bruise like pain which the patient refers to the parotid region by difficulty in chewing partly from pain and partly from suppression of salivary secretion which obliges him to drink incessantly while eating The swelling of the affected parts is more or less considerable sometimes it extends to the neck, invades the face in a manner to disfigure the patient, at other times the swell ing extends to the tonsils and adjacent regions and leads to difficulty in swal lowing "

Another excellent early description of the disease is that of Gustav Joseph ("Bemerkungen uber die vom Januar bis Marz 1864 epidemischen genuinen Ohrspeicheldrusenerkrankungen " Berl klin Wchnschr 1:297 1864) He concluded that, on the whole the disease was contagious although he was puzzled by the fact that no mumps occurred in children when "after exami nation of the oral cavity he examined the mouths of other healthy children without washing the fingers which were introduced " He thought that the opening of Steno s duct was the portal of entry

5 LAVERAN A Du diagnostic et de la prophylaxie des oreillons chez l adulte et en particulier de l orchite ourlienne Bull et mém Soc méd d hôp de Paris 15 61 1879 (Séance de 10 mai 1878)

Although the occurrence of orchitis with mumps had been known since Hippocrates this article by Laveran is one of the first modern accounts Laveran

2 DUNCAN Andrew Report presented to the Royal College of Physicians of Edinburgh respecting the contagious epidemic diseases which have prevailed in that city and its neighborhood during the year 1810 etc Edinburgh M J 7 431 1811

That mumps was long recognized as occurring in epidemics is clear from the name epidemic parotitis" Hirsch (Parotitis polymorpha" in *Handbuch der historisch geographischen Pathologie* [Erlangen Ferdinand Enke 1862] p 182) has done us the service of collecting in tabular form references to a great number of outbreaks from 1714 to 1859 One or two of these may be mentioned as examples Duncan reports on an epidemic in Edinburgh in 1810 "About the beginning of the year the most remarkable epidemic which I saw was the *cynanche parotidea* of Dr Cullen a disease which is generally *known* in England by the name of mumps That this disease arises only from a peculiar and specific contagion can I think admit of no doubt This was clearly demonstrated during the *present epidemic* For after it was introduced into some schools it affected almost all the children attending them" He noted that in this epidemic the disease was confined to children and he observed no instance of the swelling of the neck being accompanied or followed by swelling of the testis

But by no means everyone considered the disease contagious Andrew Hammersley (Observations on cynanche parotidea as it occurred in the New York State Prison during the winters of 1821 and 1822" M Repository N S 7 413 1822) the resident physician at the prison for example described a sudden outbreak of eighty cases between December 8 1821 and February 5 1822 These cases were of course in adults and in eleven instances the *salivary* gland swelling was accompanied or succeeded by an affection of one or both testes and in six more cases one or both testes were involved "independent of *any stiffness or tumour of the jaw* *Thus were it not that these cases* occurred during the rage of this epidemic and a recollection of this so common metastasis we should have been without the diagnostic mark of the complaint" As to contagion he concluded "Indeed from a survey of every thing connected with this interesting malady as it occurred at the State Prison the *idea of specific contagion can hardly be entertained*

These two reports illustrate the common occurrence of mumps in closed institutions such as schools jails and military installations (see also *Ref 8*)

3 LEITZEN E Angina parotidea J d pract Heilk *86 101 1838*

In describing an outbreak of mumps in an orphan asylum *it was noted that* six cases appeared in the last four days of April Among some students who were in contact with these patients the first case of mumps did not appear *until* May 16 after an interval of about 18 days which corresponds well with modern average estimates of the incubation period (Ref 13) F Roth ("Ueber die Incubation und Uebertragbarkeit der Parotitis epidemica" *Munchen med* Wchnschr 33 345 1886) reviews the older reports on the incubation period and describes a case in which a doctor in contact with mumps made daily visits to a patient who came down after 18 days with the disease although the doctor himself remained well Roth reports this as a case of indirect transmission As to the period of contagion of mumps Rendu ("*De la periode de*

testes vulva breast joints heart eye and ear "One would be surprised if under these conditions the brain and its coverings remained protected" They report a number of cases with meningeal symptoms with paralyses or aphasia and they regard the lesion as a meningoencephalitis G N Ackers ("Parotitis complicated with meningitis" Am J Dis Child 6 399 1913) reviewed the subject in 1913 and reported 2 cases but had no idea of a viral etiology nor did R L. Haden ("The cerebral complications of mumps" Arch Int Med 23 737 1919) who observed 9 cases in an army camp among 476 patients admitted to hospital for mumps E M Holden A Y Eagles and J E Stevens ("Mumps involvement of the central nervous system" J.A M A 131 382, 1946) also from an army camp but in World War II deliberately sought, by clinical scrutiny and lumbar puncture for evidence of meningoencephalitis in 100 consecutive cases of mumps "Thirty three cases showed clinical signs of meningoencephalitis 28 of these showed abnormal spinal fluid" J W Brown H B Kirkland and G E Hein ("Central nervous system involvement during mumps" Am J M Sc 215 434 1948) obtained similar results and remark "It seems reasonable to believe that every patient with mumps is subject to the neurotropic effects of this virus" Indeed L. W Kane and J F Enders ("Immunity in mumps III The complement fixation test as an aid in the diag nosis of mumps meningoencephalitis" J Exper Med 81 137 1945) have shown that acute aseptic meningoencephalitis in patients with no clinical evi dence of mumps may be due to the specific agent of mumps Earlier literature on this point is summarized by Wesselhoeft (*op cit* p 324) C B McKaig and H W Woltman ("Neurologic complication of epidemic parotitis" Arch Neurol & Psychiat 31:794 1934) in a useful paper summarize with litera ture the various types of lesion which may occur these they classify as mye litis psychiatric disorders meningitis encephalitis neuritis neuro-ophthalmic complications and complications affecting the eighth nerve As to lesions V de Lavergne P Kissel, and H Accoyer ("Les Bases anatomopathologiques de la névraxite ourlienne" Ann méd 42 327 1937) were able to find autopsy reports of only 12 fatal cases with cerebral complications of mumps No uni form lesion was described. These authors thought that they were able to produce cerebral lesions in rabbits as did M Wollstein ("Experimental mumps meningitis" J Exper Med 34 537 1921) Wollstein injected filtered mouth washings from children with mumps into the subarachnoid space of cats and obtained a transient reaction with evidences of inflammation and an increase of *polynuclear* cells and globulin One is not convinced of a true mumps encephalitis W L Donohue ("The pathology of mumps encephalitis" J Pediat 19 42 1941) again reviewed the subject and reported a case He concluded that the fundamental lesion was a perivascular demyelinization similar to that seen in other postinfection encephalitides Mumps virus was first claimed to be isolated from spinal fluid through monkey inoculation by A Swan and J Mawson ("Experimental mumps transmission of the disease to monkeys attempts to propagate the virus in developing hen s eggs" Aus tralian M J 1 411 1943) and by G Henle and C L. McDougall ("Mumps meningo-encephalitis Isolation in chick embryos of virus from spinal fluid of a patient," Proc Soc Exper Biol & Med 66 209 1947) through egg culture Recent literature on the subject is reviewed by Gordon and Kilham (Ref 13)

reviews the older literature on the frequency and incidence of mumps orchitis discusses the nature of the condition and describes cases beginning with orchitis without overt parotitis "The swellings of the salivary glands and of the testicles develop under the influence of the same causes under the influence of the same morbid principle which spares sometimes the testicles and sometimes the salivary glands which finally can act on other glandular tissues such as the breast ovary and prostate Orchitis is a manifestation of mumps of the same category as the swelling of the salivary glands" Final proof of this statement had to wait until fifty years later when E W Hool, Jr S O Poole and W F Friedewald ("Virus isolation and serological studies on patients with clinical mumps, J Infect Dis 84 236 1949) isolated the virus of mumps from material obtained by orchidotomy inoculated into the amniotic sac of eight day old embryonated hens eggs Laveran discussed in detail the question of postorchitic atrophy and believed it usually to be associated with loss of libido and potentia He was convinced that mumps was contagious and as a preventive measure, advocated immediate isolation of any cases in a special hospital ward

Further authoritative discussions on mumps orchitis are to be found in Comby (*loc cit*) and in Schottmuller (*loc cit*) C Wesselhoeft (Orchitis in mumps Boston M & S J 183 425 458 491 520 1920) gives a comprehensive review of every phase of the subject with an extensive bibliography as does A Stengel Jr ("Mumps orchitis" Am J M Sc 191 340 1936) Stengel gives in tabular form the incidence of orchitis in mumps as set down by various observers The figures run all the way from 13 9 to 100 per cent In most of the large series however the incidence was not over 20 per cent

As to the lesion in mumps orchitis E A Gall ("The histopathology of acute mumps orchitis" Am J Path 23 637 1947) obtained bits of tissue during the course of orchidotomy in a large number of acute cases on the basis of which the histopathology is described Gall found considerable variation in the character and extent of the lesion but at its height the process consisted of "a diffuse lymphocytic infiltration of the interstitial tissue with focal hemorrhages and pronounced destruction of germinal epithelium He reviews the few cases reported in the literature most of which dealt with late lesions appearing in chronic orchitis However G G Smith ("Two cases of orchitis due to mumps treated by operation Boston M & S J 167 323 1912) as long ago as 1912 obtained biopsy specimens from two patients in the early days of mumps orchitis Grossly the testicles were greatly enlarged and appeared intensely inflamed Histological examination by Dr S Burt Wolbach was in accord with that reported by Gall

6 LANNOIS M and LEMOINE G Des manifestations méningitiques et cérébrales des oreillons Arch de neurol 11 1 1886

Cerebral manifestations with mumps had long been recognized Hamilton (Ref 1) is credited with first reporting a death because of a cerebral accident but the account leaves one in doubt as to just what happened Lannois and Lemoine review other early case reports which are all unsatisfactory because of course there was no lumbar puncture nor was there any autopsy They point out that mumps must be regarded not as a local affection of the parotid but as a generalized infection implicating not only salivary glands but also

We have already alluded to outbreaks of mumps in closed groups (Ref 2) but this tendency was exquisitely shown during World War I by the tremendous epidemics which occurred in recruits assembled at some of the army cantonments In the outbreak here described among approximately 18 000 men there were 5 756 cases an incidence of 32 per cent At the peak of the epidemic as many as 140 soldiers with mumps were admitted to hospital on one day The writer and his associates made many important observations Suppuration occurred in only one case and that was questionable Among 4 397 cases there were 611 or 13 91 per cent with orchitis Fourteen cases of a symptom complex of nausea and anorexia with pain and tenderness in the epigastrium were interpreted as pancreatitis It is of interest that in this huge series no cases of encephalitis are mentioned The writer failed to grow an organism from puncture material of the parotid gland Interesting statistics of all sorts are presented In World War II also there was trouble with mumps (H C McGuiness and E. A Gall "Mumps at army camps in 1943" War Med 5 95 1944) and the subject is also reviewed by C Wesselhoeft and C F Walcott (Mumps as a military disease and its control" War Med 2:213 1942)

9 SIMONIN La Pancréatite ourlienne étude clinique Bull et mém Soc méd. d hôp de Paris 20 928 1903

Pancreatitis in association with mumps had been vaguely talked about from the beginning of the nineteenth century and the early papers with possible bearing on the subject are listed by L W Farnam ("Pancreatitis following mumps report of a case with operation" Am J M Sc 163 859 1922) Cuche (Localisation de l infection ourlienne sur le pancréas" Bull et mém Soc méd d hôp de Paris 14 340 1897) is given credit for arousing modern interest in the subject, but his paper is simply a brief note stating that he had observed tenderness on pressure in the epigastrium 20 times in 26 cases of mumps Simonin goes further and reports in detail 10 cases of mumps with severe epigastric pain (*douleur pancréatique*) and tenderness often with fever and prostration which he interpreted not unreasonably as pancreatitis G H Lemoine and F Lapasset ("Un cas de pancréatite ourlienne avec autopsie" Bull et mém Soc méd d hôp de Paris 22 640 1905) report a case in which pancreatitis was confirmed at autopsy and in Farnam s patients pancreatitis was found at laparotomy The whole subject is reviewed by Wesselhoeft (*op cit* p 321)

10 JOHNSON Claud D and GOODPASTURE Ernest W An investigation of the etiology of mumps J Exper Med 59 1 1934

Johnson and Goodpasture review the literature on attempts to establish the etiology of mumps (see Ref 7) and they conclude "One gains no conviction that anyone has unquestionably succeeded in inducing mumps experimentally or has demonstrated the true etiological agent of this disease" They then describe their own now classical experiments in which they definitely reproduced mumps in monkeys by injection of unfiltered saliva from mumps patients in the early stages directly into the parotid ducts "The infectious agent which we have obtained from the saliva of patients in the early stages of mumps presents characteristics of a filterable cytotropic virus having a predilection for the parenchymal cells of the parotid glands of *rhesus* monkeys The virus is free of demonstrable micro-organisms it is filterable and resistant to drying and glycer

7 WOLLSTEIN Martha An experimental study of mumps J Exper Med 23 353 1916

As was the ca e with most viral infections they were at first attributed to ordinary bacteria Wollstein refers to the early bacteriological studies in mumps and to the claims made for various cocci which different observers isolated from mumps cases As recently as 1919 Russell Haden a careful worker (The bacteriology of mumps report of findings at Camp Lee Am J M Sc 158 698 1919) concluded that "mumps is probably caused by a gram positive diplo coccus and not by a filterable virus He had isolated this coccus from blood spinal fluid and lymph nodes of patients with mumps and had produced orchitis in rabbits by injection of cultures And yet his conclusions are now shown to be erroneous S Granata ("Sulle etiologia degli orecchioni da virus filtrable Med ital Napoli, 6 647 672 1908) seems to have been the first to consider seriously a filtrable agent as the cause of mumps but his experiments on rabbits with filtrates of saliva seem inconclusive C Nicolle and E Conseil ("Essai de reproduction expérimentale des oreillons chez le singe" Compt rend Acad d sc 157 340 1913) inoculated material aspirated from the parotid glands of patients with mumps into the parotids of three monkeys They produced a reaction but "the disease is ordinarily reduced in the animal to a fever of 4 to 7 days duration the general symptoms are slight or absent and swelling of the parotid is usually undetectable" Wollstein was then the first to make a serious systematic study of the effects of filtrates Mouth wash ings from patients with mumps were filtered through Berkefeld candles and in jected into the parotid glands and testes of cats After 6 or 7 days tenderness and swelling appeared in the inoculated areas lasting in the parotid 2–5 days in the testis 10–14 days The leukocytes rose markedly Wollstein was also able to transmit the disease from cat to cat Control experiments were negative Histologically "the most marked changes appeared coincidently with the third and fourth transfers In some examples the glands showed infiltration of the interlobular connective tissue with mononuclear and a few polynuclear cells in addition to the edema The epithelium of the acini was swollen and cloudy in these instances There were also constant changes in the testis Wollstein did not claim in this paper however that she had reproduced mumps but said "Whether this active material is a microorganism and if so whether it is the specific microbic cause of parotitis or mumps remains to be ascertained In a later paper ("A further study of epidemic parotitis J Exper Med 28 377 1918) Wollstein used material from adults (soldiers) and obtained the same results "The virus of parotitis was detected most readily in the saliva during the first 3 days of the disease less easily on the 6th day and not at all on the 9th day It was detected also in the blood of patients who showed marked con stitutional symptoms and in the saliva of a case of recurrent mumps at the period of enlargement of the parotid glands It was not detected in the cerebrospinal fluid" Finally Wollstein published a summary of all her work ("An experimental study of parotitis" J A M A 71:639 1918)

8 BADIN M J The epidemic of mumps at Camp Wheeler October 1917–March 1918 Arch. Int Med 22:354 1918

ports the clinical experience that a definite attack of mumps renders a person resistant to a second attack

12 JOHNSON C D and GOODPASTURE E W The histopathology of experimental mumps in the monkey *Macacus rhesus* Am J Path. 12 495 1936

Since patients very rarely die from mumps there has been little opportunity to study the pathology of the lesions Johnson and Goodpasture give a critical review of the scattered observations in the literature on the changes in the parotid. They construct a composite picture from these reports of necrosis of glandular epithelium desquamation of epithelial cells with serous and cellular infiltration Next they made careful gross and histological studies of the experimental lesions in monkeys "The essential lesion is the result of a specific action of mumps virus on acinar epithelial cells in focal areas resulting in degeneration and necrosis of the affected cells The inflammatory cellular response is secondary to the specific injury and consists of an infiltration of the area by mononuclear phagocytic cells and later by various types of lymphocites Inclusions are described in the affected epithelial cells and they are interpreted as specific"

13 GORDON John E and HEEREN Ralph K. The epidemiology of mumps Am J M Sc 200 412, 1940

In this valuable review all phases of the subject—pathogenesis spread of virus carriers mode of transmission, portal of entry period of infectiousness communicability immunity mortality rates and other matters—are discussed, with bibliography The subject is brought up to date by a further review (J E. Gordon and L. Kilham "Ten years in the epidemiology of mumps" Am J M Sc 218 338 1949) in which special stress is placed on the newer laboratory aids

14 ENDERS John F and COHEN Sidney Detection of antibody by complement fixation in sera of man and monkey convalescent from mumps Proc. Soc Exper Biol & Med 50 180 1942

The appearance of outbreaks of mumps in the armed forces in World War II together with the development of new techniques of virus study led to a tremendous burst of work on the disease The huge and for the most part, highly technical literature on the subject is not suitable for detailed notice in this bibliography However we have tried to select papers in which a new development is described or in which an outstanding advance in knowledge is made

Enders and Cohen were the first to develop a complement fixation test for mumps Using Goodpasture's technique they produced mumps in monkeys As antigen for complement fixation they used suspensions of ground up monkey parotid glands excised at the height of the disease "It is evident however that the extensive application of the test will depend upon the discovery of a more readily available and cheaper source of antigen" Nonetheless within 3–5 days following the acute stage a high titer of complement fixing antibody was present After a month or so the titer declined but then appeared to remain constant for months Enders ("Observations on immunity in mumps" Ann Int Med. 18 1015 1943) described the results of complement fixation tests in greater

mation, it causes a lesion which is primarily a degeneration and necrosis of the parenchymal cells of the parotid and it confers immunity to reinoculation There is good evidence we consider that this virus is the cause of mumps The clinical disease induced in *M rhesus* monkeys is analogous to mumps in the human being The histology of the parotitis of human mumps is as yet undetermined but the lesions of the experimental disease are quite comparable to those found in the specific orchitis of mumps In order to prove the matter to the hilt Johnson and Goodpasture ("The etiology of mumps" Am J Hyg 21 46 1935) attempted to produce the disease in human volunteers by introducing into the buccal cavity virus which had been carried through fourteen successive generations in monkeys "The success of the experiment recorded in this paper in inducing typical clinical mumps in six and questionable mumps in three out of a total of 13 presumably susceptible persons is to us conclusive evidence that we are dealing with the true causative agent The incubation period varied from 18 days which is the average incubation period to 33 days The disease was characterized by the unilateral or bilateral enlargement of the parotid glands with pain and swelling of the face over the gland and a mild fever The saliva from a typical case was recovered and with it the experimental disease in monkeys was reproduced The secret of success seems to have been the injection of large amounts of material directly into Stenson s duct

G M Findlay and L P Clarke ("The experimental production of mumps in monkeys" Brit J Exper Path 15 309 1934) soon confirmed this work and found that injection of the virus into the tunica vaginalis of monkeys caused a non suppurative orchitis Mice rats and guinea pigs inoculated intracerebrally did not develop any symptoms C Levaditi R Martin A Bonnefoi and R Schoen reported similar results ("Contribution à l etude étiologique des oreillons" Bull Acad de méd Paris 114 251 1935)

11 JOHNSON Claud D and GOODPASTURE Ernest W Experimental immunity to the virus of mumps in monkeys Am J Hyg 23 329 1936

A F Hess ("A protective therapy for mumps" Am J Dis Child 10 99 1915) appears to have been the first to attempt the prevention of mumps by passive immunization—the injection into susceptibles of human convalescent serum Among seventeen "susceptible children who were exposed to mumps no case of the disease occurred following 6–8 cc of whole blood L H Barenberg and J Ostroff ("Use of human blood in protection against mumps" Am J Dis Child 42 1109 1931) had somewhat less good results—39 per cent incidence among the untreated against 15 per cent among those who received treatment They also thought that mumps was markedly attenuated by this form of serotherapy Cambessédès ("L Emploi du sérum de convalescents dans les oreillons" Ann d'hyg pub N S 11 83 1933) also reports the use of convalescent serum as a useful prophylactic

Johnson and Goodpasture subjected the question to more exact experimental trial with mumps produced in monkeys First of all they found that "attempts to confer passive immunity to intraparotid infection by injections of serum from persons immune to mumps have with rare exceptions failed" Overt infections however seemed to confer an invariable immunity to a second attack There was also evidence that subclinical infection conferred immunity All this sup-

ports the clinical experience that a definite attack of mumps renders a person resistant to a second attack

12 JOHNSON C D and GOODPASTURE E W The histopathology of experimental mumps in the monkey *Macacus rhesus* Am J Path **12**:495 1936

Since patients very rarely die from mumps there has been little opportunity to study the pathology of the lesions Johnson and Goodpasture give a critical review of the scattered observations in the literature on the changes in the parotid They construct a composite picture from these reports of necrosis of glandular epithelium desquamation of epithelial cells with serous and cellular infiltration Next they made careful gross and histological studies of the experimental lesions in monkeys "The essential lesion is the result of a specific action of mumps virus on acinar epithelial cells in focal areas resulting in degeneration and necrosis of the affected cells The inflammatory cellular response is secondary to the specific injury and consists of an infiltration of the area by mononuclear phagocytic cells and later by various types of lymphocites Inclusions are described in the affected epithelial cells and they are interpreted as specific

13 GORDON John E and HEEREN Ralph K The epidemiology of mumps Am J M Sc **200** 412 1940

In this valuable review all phases of the subject—pathogenesis spread of virus carriers mode of transmission portal of entry period of infectiousness communicability immunity mortality rates and other matters—are discussed with bibliography The subject is brought up to date by a further review (J E Gordon and L Kilham "Ten years in the epidemiology of mumps" Am J M Sc **218**:338 1949) in which special stress is placed on the newer laboratory aids

14 ENDERS John F and COHEN Sidney Detection of antibody by complement fixation in sera of man and monkey convalescent from mumps Proc Soc Exper Biol & Med **50** 180 1942

The appearance of outbreaks of mumps in the armed forces in World War II together with the development of new techniques of virus study led to a tremendous burst of work on the disease The huge and for the most part highly technical literature on the subject is not suitable for detailed notice in this bibliography However we have tried to select papers in which a new development is described or in which an outstanding advance in knowledge is made

Enders and Cohen were the first to develop a complement fixation test for mumps Using Goodpasture s technique they produced mumps in monkeys As antigen for complement fixation they used suspensions of ground up monkey parotid glands excised at the height of the disease "It is evident however that the extensive application of the test will depend upon the discovery of a more readily available and cheaper source of antigen" Nonetheless within 3–5 days following the acute stage a high titer of complement fixing antibody was present After a month or so the titer declined but then appeared to remain constant for months Enders ("Observations on immunity in mumps" Ann Int Med **18**:1015 1943) described the results of complement fixation tests in greater

detail In tests of humans antibody occurred in about 92 per cent of the sera of those giving a positive history of mumps But 50 per cent of the sera from people who gave no history of mumps was also positive This the writers interpret as evidence of the frequency of inapparent or "silent infection On the other hand it was concluded that most of those who gave a negative reaction were susceptible

The significance of the complement fixation test was further elaborated by E P Maris J F Enders J F Stokes Jr, and L W Kane ("Immunity in mumps IV The correlation of the presence of complement fixing antibody and resistance to mumps in human beings" J Exper Med 84 323 1946) who showed that with very rare exceptions individuals giving positive complement fixation tests for mumps are resistant to infection by natural exposure" and that a positive complement fixation indicates previous infection with this virus The complexity of the subject is revealed however by the later work of G Henle G Harris and W Henle ("The reactivity of various human sera with mumps complement fixation antigens J Exper Med 88 133 1948) who found that *there are two serologically distinct complement fixing antigens against which* antibodies arise at different times

Using suspensions of infected parotid Enders also developed a skin test At the site of injection "in nearly 100 per cent of those giving a history of mumps an erythematous reaction occurred after 24 to 48 hours The group giving no history of mumps revealed about equal numbers of negative and positive reactors" Both these tests were subsequently investigated for rapid determination of susceptibility or immunity to mumps so important in epidemiological problems Thus details of the significance of the skin test were worked out by J F Enders L W Kane E P Maris and J Stokes Jr ("Immunity in mumps V The correlation of the presence of dermal hypersensitivity and resistance to mumps J Exper Med 84 341 1946) and by G Henle *et al* (Studies on the prevention of mumps I The determination of susceptibility" J Immunol 66:535 1951) They showed that clinically inapparent infections were frequent and conferred immunity as well as an overt attack

An interesting and authoritative review of the immunological problems of mumps is that of J F Enders ("Mumps technique of laboratory diagnosis tests for susceptibility and experiments on specific prophylaxis" J Pediat 29 129 1946)

15 GELLIS S S McGUINNESS A C and PETERS M A study on the prevention of mumps orchitis by gamma globulin Am J M Sc **210** 661 1945

Little if anything is available in the wav of therapy for established mumps other than symptomatic measures Gellis and co-workers have obtained suggestive evidence that convalescent human gamma globulin in doses of 20 cc reduced the incidence of orchitis from 27 4 to 7 8 per cent Normal serum gamma globulin however in 50 cc doses was not followed by a reduction in incidence

16 HABEL Karl Cultivation of mumps virus in the developing chick embryo and its application to the studies of immunity to mumps in man Pub Health Rep **60** 201 1945

Habel using an emulsion of parotid glands from monkeys infected with mumps (Ref 10) inoculated the yolk sac the amniotic sac and the allantoic sac of chick embryos He succeeded in growing virus in all these situations as tested by monkey inoculation complement fixation tests and neutralization tests The chick embryo virus turned out to be a suitable antigen for complement fixation and for human skin testing J H Levens and J F Enders ("The hemagglutinative properties of amniotic fluid from embryonated eggs infected with mumps virus" Science 102:117 1945) soon confirmed Habel s work they were unable to demonstrate antigen in the yolk sac although it was present in other tissues They also showed that the amniotic fluid of infected eggs agglutinated fowl red cells in a manner analogous to influenza and other viruses a reaction most useful for rapid diagnosis of mumps thus hemagglutination is inhibited by the sera of man and monkey convalescent from mumps W I B Beveridge P E Lind and S G Anderson ("Mumps I Isolation and cultivation of the virus in the chick embryo" Australian J Exper Biol & M Sc 24 15 1946) in the following year reported successful growth in the chick embryo after either yolk sac or amniotic inoculation of human saliva from patients early in the course of mumps G R Levmister and T G Ward (Direct isolation of mumps virus in chick embryos" Proc Soc Exper Biol & Med 65:346 1947) using fresh saliva treated with penicillin and streptomycin were able to infect directly the amniotic sac of chick embryos with material from eight of nine patients with mumps

Aside from the monkey (Ref 10) the chick embryo seems to be the only animal which has so far been found susceptible to mumps

17 STOKES J ENDERS J F MARIS E and KANE L W Immunity in mumps VI Experiments on the vaccination of human beings with formolized mumps virus J Exper Med 84:407 1946

In certain situations such as assemblies of young soldiers in camps or in schools it seems of the utmost importance to prevent the spread of mumps To this end the writers experimented with attempts to produce active immunity in susceptible people by vaccination with (killed) formol inactivated mumps virus They concluded that this procedure led to increased resistance in about 50 per cent of children K Habel (Vaccination of human beings against mumps vaccine administered at the start of an epidemic. I Incidence and severity of mumps in vaccinated and control groups Am J Hyg 54 295 1951 "II Effect of vaccination upon the epidemic" *ibid* p 312) using formolized infected allantoic fluid vaccinated a large number of individuals in army camps He concluded that vaccination at the beginning of an epidemic in a highly susceptible population caused a reduction in the incidence of mumps Also the mumps seemed less severe in the vaccinated and there was less tendency toward orchitis He also thought that there was evidence that vaccination controlled the severity of an incipient epidemic of mumps It was found by J F Enders *et al* ("Attenuation of virulence with retention of antigenicity of mumps virus after passage in the embryonated egg" J Immunol 54:283 1946) that by repeated passages in the embryonated egg mumps virus had lost the capacity to produce parotitis in monkeys although it still immunized the animal against a subsequent inoculation with virulent virus It

also seemed incapable of producing mumps in susceptible humans when sprayed into the oral cavity G Henle *et al* (Studies on the prevention of mumps IV The effect of oral spraying of attenuated virus" J Immunol 66 579 1951) also felt that oral spraying of children with active attenuated mumps virus probably produced active immunity as measured by the appearance of antibodies and by clinical exposure

Thus real progress seems to be in the making

18 WEIL M L BEARD Dorothy SHARP D G and BEARD J W Purification and sedimentation and electron micrographic characters of the mumps virus, Proc Soc Exper Biol & Med 68 309 1948

The writers measured particle size of mumps virus in the electron microscope The great variations in size are well shown in their photographs "The shape of the formolized virus was judged to be spherical and flattened" Electron micrographic images have a diameter of 190 ± 42 mμ I M Dawson and W J Elford ("The investigation of influenza and related viruses in the electron microscope by a new technique J Gen Microbiol 3 298 1949), using a method in which virus is adsorbed on the membranes of laked fowl red cells for examination in the electron microscope got a value for mumps virus size of 179 ± 28 Thus mumps virus evidently is relatively large

19 KILHAM L Isolation of mumps virus from the blood of a patient Proc Soc Exper Biol & Med 69 99 1948

Kilham was the first to make a plausible claim of having isolated mumps virus from circulating blood "Virus of mumps was isolated from blood of a patient with bilateral parotid swelling through cultivation in embryonated eggs Inhibition of hemagglutination and complement fixation tests confirmed the clinical diagnosis and identified the agent as mumps virus A very small quantity of plasma sufficed This finding strongly supports the view that mumps is primarily a general infection with localization in various situations

20 MORGAN H R ENDERS J F and WAGLEY P F A hemolysin associated with the mumps virus J Exper Med 88 503 1948

Levens and Enders in unpublished experiments had noticed hemolysis of suspensions of chicken erythrocytes exposed to amniotic or allantoic fluids derived from chick embryos infected with mumps virus The present paper gives the results of systematic studies of this hemolytic factor The hemolysin is specific and is inhibited by serum of man and monkey convalescent from mumps Many other features are discussed

21 HENLE G DEINHARDT F and GUARDI A Cytolytic effects of mumps virus in tissue cultures of epithelial cells Proc Soc Exper Biol & Med 87 386 1954

Johnson and Goodpasture (Ref 12) had noted years previously that mumps virus produced necrosis of parotid epithelium The present writers using cultures of HeLa or monkey kidney epithelial cells inoculated with mumps virus produced interesting effects which they regarded as cytolytic "Cytolysis was specifically prevented by human mumps convalescent and postvaccination sera"

WHOOPING COUGH

Section 31

WHOOPING COUGH

IN THE concluding section of Volume 1 of this bibliography we have taken the liberty of discussing pertussis as a disease of unknown etiology since there are a number of facts which throw an element of doubt on the Bordet Gengou organism as the sole cause of the disease These are as follows (1) the isolation in tremendous numbers of other organisms from cases of pertussis as noted by Jochmann and Krause (Ref 3), (2) Bordet and Gengou s arbitrary dismissal of all other claims (Ref 5) (3) the confused state of im munity reactions which apparently concern the Bordet bacillus but do not rule out another agent (4) the solid immunity and the frequency in early childhood suggest a virus disease (5) the inclusion bodies of McCordock and others which suggest a virus disease (Ref 9) (6) the occurrence of interstitial pneumonia and of encephalitis resembling those seen in viral diseases such as influenza and measles (7) it seems improbable that one hemophilic bacillus (*B influenzae*) should be a notable secondary invader whereas another rather similar organism should be a highly specific pathogen (8) until 1921 equally consistent claims were made for *B influenzae* as the cause of influenza F G Blake T M Rivers and J G Small ("The etiology of influenza" in *Epidemic Respiratory Disease* [St Louis C V Mosby 1921] chap i), representing gen eral opinion in America say "Consideration of all the evidence available makes it seem highly probable that B influenzae is the specific etiological agent of epidemic influenza Blake and Cecil (Ref 6) later thought that they had pro duced influenza in monkeys by inoculation with the bacillus

In favor of the Bordet Gengou bacillus as the cause of whooping cough are (1) its frequent presence in the sputum in large numbers especially in early cases, (2) its presence among the cilia in the respiratory tract (Ref 7) (3) the reproduction of a disease apparently identical with pertussis in man in mon keys (Ref 10) and (4) the protection against the disease conferred by vacci nation (Ref 11)

The reader may make his choice we have tried to review the literature in an unbiased way

The classical textbook account of the disease is that of Georg Sticker (*Der Keuchhusten* [Vienna Alfred Holder 1896]) written just before the discovery of the Bordet-Gengou bacillus and containing an extensive bibliography of older references The standard modern treatise is J H Lapin s book *Whooping Cough* (Springfield Ill Charles C Thomas 1943) which has chapters on every phase of the disease with extensive bibliographies finally one should mention the chapter by Louis W Sauer "Whooping cough" in Brennemann s *Practice of Pediatrics* ed McQuarrie (Hagerstown W F Prior n d) chapter 34 as a good brief review of the subject

1 WATT Robert Treatise on the history nature and treatment of chin cough Glasgow John Smith & Son 1813

While whooping cough has been recognized for hundreds of years even rela tively recent accounts are of little value Thus as late as 1769 John Millar s ac-

count (*Observations on the Asthma and on the Hooping Cough* [London T Cadel 1769]) leans heavily on humoral doctrines although there is a good clinical description of the disease Robert Watt wrote one of the first books on the subject, saying in justification "The disease in fact has been very generally abandoned by the profession and left as Willis observes to the management of old women and quacks" Watt regarded whooping cough as contagious "The chincough is a highly infectious disease and seems always to arise from a specific contagion" (p 25) Predisposition immunity to second attacks and relation to climate and season are next discussed followed by an accurate and detailed clinical analysis "There is hardly any disease for which Chincough can be mistaken" As to confusion with asthma "the one proceeds from a specific contagion and occurs only once in the same individual The other is often an hereditary disease often proceeds from ordinary causes and when it does appear it is apt to continue for life The one is a disease as we have seen al most peculiar to the ages below puberty while the other seldom occurs till manhood and most generally indeed not till the decline of life and sometimes not till old age" (p 76) Several cases are reported with autopsies The first two Robert Watt and Janet Watt are evidently the author s children at autopsy what was clearly bronchopneumonia was the outstanding finding The long section on therapy is hardly worth reviewing numerous medicines and treat ments are described in contemporary fashion—opium canthandes asafoetida hemlock castor oil of amber etc

2 EDMONSTONE Henry Brief outline of a plan for diminishing the prevalence and fatal tendency of hooping-cough Edinburgh M & S J 7 16 1811

"The mortality which hooping-cough produces among the children of the country is a perpetual source of sorrow and anxiety to all classes of the com munity in many of those who escape the immediate effect [death] it lays the foundation of complaints that prove equally destructive or it induces a predisposition to pulmonary affections which otherwise might never have existed I would therefore propose that persons affected should wear some conspicuous article of dress by which they might be easily discerned at a distance and an opportunity by that means offered to all who might be so in clined of keeping beyond the sphere of contagion A red hat, cap or ribbon for example might be worn for this purpose I appeal therefore with confi dence to parents guardians to give it their support."

3 JOCHMANN Georg, and KRAUSE Paul Zur Aetiologie des Keuch hustens Ztschr f Hyg u Infectionskr 36 193 1901

The writers first review numerous claims for various bacteria as the cause of whooping cough Those dealing with Protozoa or cocci need not detain us but in view of the work of Bordet and Gengou (Ref 5) some of those dealing with bacilli require analysis Carl Burger ("Der Keuchhustenpilz," Berl. klin Wchnschr 20 7 1883) as early as 1883 described the presence of a tiny bacillus in enormous numbers in the sputa of whooping cough patients It was not found in other conditions E Czaplewski and R Hensel (Bacteriologische Untersuchungen bei Keuchhusten" Deutsche med Wchnschr 23 586 1897) examined fresh sputum brought up during a paroxysm of coughing in early

Section 31

WHOOPING COUGH

IN THE concluding section of Volume 1 of this bibliography we have taken the liberty of discussing pertussis as a disease of unknown etiology since there are a number of facts which throw an element of doubt on the Bordet Gengou organism as the sole cause of the disease These are as follows (1) the isolation in tremendous numbers of other organisms from cases of pertussis as noted by Jochmann and Krause (Ref 3) (2) Bordet and Gengou s arbitrary dismissal of all other claims (Ref 5) (3) the confused state of immunity reactions which apparently concern the Bordet bacillus but do not rule out another agent (4) the solid immunity and the frequency in early childhood suggest a virus disease (5) the inclusion bodies of McCordock and others which suggest a virus disease (Ref 9) (6) the occurrence of interstitial pneumonia and of encephalitis resembling those seen in viral diseases such as influenza and measles (7) it seems improbable that one hemophilic bacillus (*B influenzae*) should be a notable secondary invader whereas another rather similar organism should be a highly specific pathogen (8) until 1921 equally consistent claims were made for *B influenzae* as the cause of influenza F G Blake T M Rivers and J G Small ("The etiology of influenza" in *Epidemic Respiratory Disease* [St Louis C V Mosby 1921] chap 1) representing general opinion in America say "Consideration of all the evidence available makes it seem highly probable that B influenzae is the specific etiological agent of epidemic influenza" Blake and Cecil (Ref 6) later thought that they had produced influenza in monkeys by inoculation with the bacillus

In favor of the Bordet Gengou bacillus as the cause of whooping cough are (1) its frequent presence in the sputum in large numbers especially in early cases (2) its presence among the cilia in the respiratory tract (Ref 7) (3) the reproduction of a disease apparently identical with pertussis in man in monkeys (Ref 10), and (4) the protection against the disease conferred by vaccination (Ref 11)

The reader may make his choice we have tried to review the literature in an unbiased way

The classical textbook account of the disease is that of Georg Sticker (*Der Keuchhusten* [Vienna Alfred Holder 1896]) written just before the discovery of the Bordet Gengou bacillus and containing an extensive bibliography of older references The standard modern treatise is J H Lapin s book *Whooping Cough* (Springfield Ill Charles C Thomas 1943) which has chapters on every phase of the disease with extensive bibliographies finally one should mention the chapter by Louis W Sauer "Whooping cough," in Brennemann s *Practice of Pediatrics* ed McQuarrie (Hagerstown W F Prior n d) chapter 34 as a good brief review of the subject

1 WATT Robert Treatise on the history nature and treatment of chin cough Glasgow *John Smith & Son* 1813

While whooping cough has been recognized for hundreds of years even relatively recent accounts are of little value Thus as late as 1769 John Millar s ac

cough Bordet and Gengou were able to "find in considerable quantity the microbe of whooping cough which in favorable cases was present in almost pure culture" If specimens are obtained later in the disease the specific bacilli are scarce and there are numerous other banal organisms present

Bordet and Gengou tell of their first experience in 1900 with a five month-old infant with whooping cough "One of us was able to collect from the first crisis of typical cough a bit of whitish exudate unmixed with saliva Microscopic examination after staining showed that this exudate contained in enormous numbers a little bacterium ovoid in shape sometimes slightly elongated sometimes short to the point of resembling a coccus but in general rather constant in appearance Gram stain was negative The organism was present in such abundance and with a purity so perfect that one could not deny a causal relation between this infection and whooping cough" Bordet and Gengou were at first unable to obtain growth on various artificial media, but later they devised a hemoglobin-containing medium on which they were able to cultivate their organism They describe the cultural appearance "These colonies were bluish or grayish slightly raised in the center always a little diaphanous especially toward the borders almost transparent in the yellow cultures where they appeared as little rose-colored drops Under the microscope one saw a very small microbe not taking the Gram stain It was easy to establish that we were in the presence of an organism identical with or very similar to that found by Pfeiffer in influenza which other bacteriologists emphasized in whooping cough and even considered as the specific microbe" They refer to the work of Jochmann and Krause (Ref 3) "who described this organism very exactly and mentioned the need for hemoglobin" There follows a lengthy but unclear discussion on the actual relation of this microbe to their own "In brief this organism [of Jochmann and Krause] so like that described by Pfeiffer as provoking influenza is not the agent of whooping cough" Bordet and Gengou now (1906) isolated from a baby with whooping cough as they had in 1900 a similar bacterium which grew with great delicacy on their medium "The comparison in culture of this parasite with the microbe of influenza shows that these two species are essentially different," as shown by comparison of cultures The authenticity of this microbe as the causal agent of whooping cough "rests largely on serological reactions The serum of individuals not having had whooping cough does not agglutinate the microbe The serum of children recently cured of this disease possesses agglutinative power of moderate degree but it is constant and manifest" Bordet and Gengou employed the method of complement fixation Emulsions of whooping-cough bacilli were used as antigens "As for the microbe so like that described in influenza it behaves with whooping cough serum as if it were in the presence of normal serum The findings relative to the etiology of whooping cough seem to us thus well established we hope to make known shortly the results of trials of serotherapy or active immunization" In another paper ("Note complémentaire sur le microbe de la coqueluche" Ann Inst Pasteur 21 720 1907) Bordet and Gengou describe their organism further lay down criteria of differentiation from the influenza bacillus and discuss agglutination tests Whereas the organism was regularly clumped by artificial sera (horse) "unhappily the sera of children sick with or convalescent from pertussis are extremely inconstant from the point

cases of whooping cough in an epidemic at Konigsberg They found small rods with *rounded* ends *in huge* numbers in thirty consecutive cases The bacteria resembled influenza bacilli but grew without addition of blood to the medium No lesions were produced in animals By the constant finding [of these bacilli] we are forced to the conclusion that the bacterium in question is the cause of whooping cough We believe that Burger described our bacilli" H Koplik (The bacteriology of pertussis" Bull Johns Hopkins Hosp 9 79 1898) in pure culture from the sputa of early cases of whooping cough also obtained a small bacillus which grew without hemoglobin and produced no lesions in animals Without making any out and-out claims as to etiology Koplik says What significance can we attribute to the bacterium which is the theme of this paper? I doubt whether this can be solved except by direct experiment on the human subject" Jochmann and Krause themselves found three varieties of bacteria resembling influenza bacilli in size and shape in the sputa of early whooping cough cases One variety obtained in eighteen cases was Gram negative and grew only on blood agar in dewdrop colonies This organism was often present in tremendous (*massenhaften*) numbers in direct smears In fatal cases the organism was found in pure culture in bronchopneumonic foci Jochmann and Krause named this organism *Bacillus pertussis Eppendorf*

Here then are a few examples of the findings of various bacteriologists who obtained more or less pure growths of small influenza like bacilli from whooping cough Since these were obviously not all the same the only possible conclusion is that whooping cough paves the way for a tremendous invasion by a group of bacteria which have some resemblances among themselves and all of which are somewhat similar to influenza bacilli Since it is now known that the influ enza bacilli are only secondary invaders in influenza on a soil prepared by a virus infection the question is naturally raised whether the same state of affairs does not exist in pertussis This thought is especially pertinent in view of the widespread belief that the bacillus of Bordet and Gengou is the cause of whooping cough (Ref 5)

4 NEURATH Rudolph Die nervosen Komplicationen und Nachkrank heiten des Keuchhustens Arb a d neurol Inst an d Wiener Univ 11 258 1904

This monograph of over a hundred pages deals with every phase of the neuro logical complications and sequels of whooping cough Convulsions meningitis cerebral palsies psychic disturbances sensory disturbances spinal cord affec tions and polyneuritis are all discussed in detail with an elaborate review of the literature and a long bibliography The writer thinks that hemorrhage from increased venous pressure is most important but the perivascular cuffing with round cells described in a number of his own autopsies raises the question of virus encephalitis

5 BORDET J and GENGOU O Le Microbe de la coqueluche Ann Inst Pasteur 20 731 1906

The authors point out that for twenty years others have made claims of having isolated the causal organism of whooping cough But none of these claims has been confirmed By paying attention to obtaining material for study early in the disease and expectorated from the depths of the lung during a paroxysm of

cough Bordet and Gengou were able to "find in considerable quantity the microbe of whooping cough which in favorable cases was present in almost pure culture" If specimens are obtained later in the disease the specific bacilli are scarce and there are numerous other banal organisms present

Bordet and Gengou tell of their first experience in 1900 with a five month-old infant with whooping cough "One of us was able to collect from the first crisis of typical cough a bit of whitish exudate unmixed with saliva Microscopic examination after staining showed that this exudate contained in enormous numbers a little bacterium ovoid in shape sometimes slightly elongated sometimes short to the point of resembling a coccus but in general rather constant in appearance Gram stain was negative The organism was present in such abundance and with a purity so perfect that one could not deny a causal relation between this infection and whooping cough" Bordet and Gengou were at first unable to obtain growth on various artificial media but later they devised a hemoglobin-containing medium on which they were able to cultivate their organism They describe the cultural appearance "These colonies were bluish or grayish slightly raised in the center always a little diaphanous especially toward the borders almost transparent in the yellow cultures where they appeared as little rose-colored drops Under the microscope one saw a very small microbe not taking the Gram stain It was easy to establish that we were in the presence of an organism identical with or very similar to that found by Pfeiffer in influenza which other bacteriologists emphasized in whooping cough and even considered as the specific microbe" They refer to the work of Jochmann and Krause (Ref 3) "who described this organism very exactly and mentioned the need for hemoglobin" There follows a lengthy but unclear discussion on the actual relation of this microbe to their own "In brief this organism [of Jochmann and Krause] so like that described by Pfeiffer as provoking influenza is not the agent of whooping cough" Bordet and Gengou now (1906) isolated from a baby with whooping cough as they had in 1900 a similar bacterium which grew with great delicacy on their medium "The comparison in culture of this parasite with the microbe of influenza shows that these two species are essentially different" as shown by comparison of cultures The authenticity of this microbe as the causal agent of whooping cough "rests largely on serological reactions The serum of individuals not having had whooping cough does not agglutinate the microbe The serum of children recently cured of this disease possesses agglutinative power of moderate degree but it is constant and manifest" Bordet and Gengou employed the method of complement fixation Emulsions of whooping-cough bacilli were used as antigens "As for the microbe so like that described in influenza it behaves with whooping cough serum as if it were in the presence of normal serum The findings relative to the etiology of whooping cough seem to us thus well established we hope to make known shortly the results of trials of serotherapy or active immunization" In another paper ("Note complémentaire sur le microbe de la coqueluche" Ann Inst Pasteur **21** 720 1907) Bordet and Gengou describe their organism further lay down criteria of differentiation from the influenza bacillus and discuss agglutination tests Whereas the organism was regularly clumped by artificial sera (horse) "unhappily the sera of children sick with or convalescent from pertussis are extremely inconstant from the point

of view of this property It often is manifest without being very intense sometimes it is even absent altogether Another paper ("L'Endotoxine coqueluche *ibid* 23 445 1909) deals with endotoxin They found that cultures injected into the guinea pigs peritoneum were highly toxic although the bacteria did not multiply and they felt that death was due to intoxication" They developed methods for extracting the "endotoxin from cultures C Fraenkel ("Untersuchungen zur Entstehung des Keuchhustens" Munchen med Wchnschr 55 1683 1908) soon sounded a conservative note While he isolated and grew the organism of Bordet and Gengou he found the serological reactions variable and doubtful and although he produced a respiratory infection in monkeys he was not certain it was whooping cough Fraenkel did not mention the experiments of Klimenko (Ref 6) and the latter chided him in a second paper (Klimenko "Zur Aetiologie des Keuchhustens" Deutsche med Wchnschr 34 2030 1908)

What then is the significance of the organism of Bordet and Gengou? One *should note that they dismiss abruptly all previous work although* as reviewed by Jochmann and Krause many workers had found various small bacilli some resembling influenza bacilli some Gram negative in practically pure culture in whooping cough Why is the bacillus of Bordet and Gengou entitled to more consideration as a causal agent? Indeed Bordet and Gengou themselves had trouble differentiating it from other influenza bacillus like "bacteria" As far as the serological tests by the method of complement fixation are concerned confirmation of their results has failed (Ref 5 Fraenkel) Indeed one wonders at the general acceptance of Bordet and Gengou s claims

6 KLIMENKO W N Die Aetiologie des Keuchhustens Experimenteller Keuchhusten Centralbl f Bakt 48 64 1908

Klimenko confirmed the finding of Bordet and Gengou s bacillus in whooping cough but he concentrated his efforts on trying to reproduce the disease in animals Injections of cultures into the bodies of rabbits and guinea pigs were without effect In monkeys on the other hand there was some fever nasal discharge conjunctivitis and diarrhea One monkey died of intercurrent infection and the Bordet Gengou bacillus was recovered from the air passages Six monkeys had a "barking" cough A female received the contents of an agar slant of culture and developed cough with recovery of the organism her cage mate developed fever and cough and the Bordet Gengou organism was recovered from the nose on the fifth tenth and twentieth days Similar results were obtained in still other animals although as a rule the reaction was "abortive" *Three dogs each receiving the growth from two agar slants remained perfectly* well In 48 young dogs there was a high incidence of infection by contact, both experimental and spontaneous featured by fever and catarrhal symptoms Animals which died or were killed all showed at autopsy inflammation in the respiratory passages The Bordet Gangou organism was recovered from all these animals

There seems no doubt that Klimenko produced a disease in dogs The question is whether it was whooping cough He says himself "How shall one designate the disease which the Bordet Gengou bacillus evokes in animals? I think *one can* call it an infectious catarrh of the air passages such a designation certain clinicians also give to whooping cough" He concludes however that

the Bordet-Gengou bacillus is undoubtedly the cause of whooping cough and that one can reproduce the disease in young dogs and monkeys

It seems to us however that it is not proved that the experimental disease was actually pertussis One must recall a similar situation with reference to the influenza bacillus which is now of course proved not to be the cause of influenza. Yet F G Blake and R L. Cecil ("The production of an acute respiratory disease in monkeys by inoculation with Bacillus influenzae" J.A M.A 74 170 1920) concluded that "the disease appears to be identical with influenza in men it seems reasonable to infer that B influenzae is the specific cause of influenza"

7 MALLORY F B., and HORNOR A. A. Pertussis the histological lesion in the respiratory tract J M Research 27:115 1913

Mallory and Hornor emphasized the presence of huge numbers of a small Gram negative bacillus presumably similar to the Bordet-Gengou organism between the cilia of the cells lining the trachea and bronchi "The location of the organism is apparently characteristic for the disease Its action seems to be largely mechanical. It interferes by its presence with the normal movements of the cilia and possibly leads to their destruction." The lesion is well pictured A little later Mallory and Hornor with F F Henderson ("The relation of the Bordet-Gengou bacillus to the lesion of pertussis" *ibid.* p 391) reported reproducing this "specific" lesion in animals with sputum and with pure cultures of the bacillus They conclude that they have fulfilled Koch s laws in relating the Bordet bacillus to whooping cough. L. J Rhea ("The comparative pathology of the tracheal and bronchial lesions produced in man by B pertussis [whooping cough] and those produced in dogs by B bronchisepticus [canine distemper]" J.M Research, 32:47 1915) however questioned the final validity of this position since he found a similar lesion in dogs infected with *B bronchisepticus* He felt that, in addition to histological examination "B pertussis must be recovered and completely identified by bacteriological as well as agglutination reactions"

8 CHIEVITZ, I and MEYER A H. Recherches sur la coqueluche Ann Inst. Pasteur 30 503 1916

The writers dissatisfied with the isolation of Bordet bacilli from pertussis patients had them cough directly at Petri plates containing appropriate media and were highly successful in obtaining growth of the organisms in question During the second week of the disease these "cough plates" which later were universally used in diagnosing pertussis were positive in 89 per cent of cases a figure which had dropped by the fourth week to 32 per cent and by the seventh week to zero A similar diagram is to be found in the article on whooping cough by L. W Sauer (in Brennemann s *Practice of Pediatrics* Vol 2, chap 34 p 7) J J Miller ("Etiology of whooping cough," J.A M.A. 100 681 1933) refers to the Danish experience with cough plates he says the method is universally accepted in Scandinavia

9 McCORDOCK H A. Intranuclear inclusions in pertussis Proc Soc Exper Biol & Med 29 1228 1932.

Not everyone was willing blindly to accept the Bordet Gengou bacillus as the cause of whooping cough F Freyer in an elaborate study of the pathology of pertussis ("Ueber die pathologische Anatomie der Lungenveranderungen beim Keuchhusten" Frankfurt Ztschr f Path 35 213 1927) described a case with intranuclear inclusions in the lung cells "signs of the presence of a peculiar virus" McCordock, however enumerated the points of resemblance between pertussis and known virus infections namely the interstitial pneumonia indistinguishable from that seen in influenza and measles and the encephalitis which also occurs following measles and influenza He pointed out that inclusion bodies are often associated with virus diseases and he found them in twelve of thirty five cases of whooping cough "The presence of intranuclear inclusions in the lungs in such a high percentage of our cases of pertussis and their in frequency in a variety of other childhood diseases suggest that the possible role of a filterable virus must be considered in this disease" Later at a meeting of the American Association of Pathologists (Am J Path 13 644 1937) McCordock stated "To date we have demonstrated them [intranuclear inclusions in pertussis] both in our St Louis material and also in sections from other cities in about 30 per cent of all cases of pertussis examined They cannot be produced by bacteria This phase of the pertussis problem can never be solved by repeating experiments with hemophilic bacteria" A R Rich ("On the etiology and pathogenesis of whooping cough" Bull Johns Hopkins Hosp 51 346 1932) also analyzes the literature on the bacillus versus a virus etiology and is unconvinced that "the Bordet Gengou bacillus represents the whole story of the etiology of whooping cough"

10 RICH A. R, LONG P H BROWN J H BLISS E A and HOLT L E Jr Experiments upon the cause of whooping cough Science, 76 330 1932

At about the time that a virus etiology was being pushed by McCordock (Ref 9) H MacDonald and E J MacDonald ("Experimental pertussis J Infect Dis 53 328 1933) on the basis of the production of whooping cough by inoculation with cultures of the Bordet Gengou bacillus and failure to produce disease in vaccinated controls or in boys inoculated with filtrates concluded that "a filter passing virus plays no rôle in the etiology of pertussis The disease is caused by the bacillus of Bordet and Gengou Active immunity is conferred by the injection of B pertussis vaccine" As only a very few subjects were used there is some question as to the MacDonalds emphatic and sweeping conclusions J M Frawley ("A study of the virus factor in whooping cough" J Pediat 16 18 1940) also failed to produce any symptoms "resembling whooping cough" in twelve children given nasal instillations of filtered washings from children with whooping cough

Rich and his colleagues report the production of a disease in chimpanzees in every way indistinguishable from whooping cough and associated with the presence of the Bordet bacilli in huge numbers in cough plates following the instillation of Bordet bacilli into the respiratory passages Filtrates of sputum from early cases of pertussis on the other hand produced only mild "febrile upper respiratory catarrhs" G S Shibley ("Etiology of whooping cough" Proc. Soc Exper Biol. & Med 31:576 1933) inoculated a chimpanzee with a strain of the Bordet bacillus subcultured long enough to rule out the associa

tion with a virus and produced in the animal what was regarded as typical whooping cough At autopsy *H pertussis* was recovered from bronchi and bronchioles but Shibley did not demonstrate "H pertussis like organisms em bedded in cilia"

The numerous transmission experiments recorded in the literature are re viewed by Lapin (*op cit* p 43) However in evaluating these experiments one should remember that washings from influenza a disease now known to be caused by a virus have also failed to produce disease in man (M J Rosenau Experiments to determine mode of spread of influenza" J.A.M.A. 73:311 1919) whereas reliable workers thought that they had produced influenza with instillations of the influenza bacillus

11 MILLER J J Jr The present status of immunization against pertussis California & West Med 53:25 1940

Early after the discovery of the Bordet-Gengou bacillus attempts were made at treatment and prophylaxis by vaccines prepared from these organisms H N Appel and O I Bloom ("Whooping cough and its treatment," Arch. Pediat 39:145 1922) give a list of the most important reports beginning in 1909 and show that variable conclusions were drawn A H Meyer M Christensen and E. Sorensen ("Whooping cough vaccination" Acta paediat 4 21 1925) in Scandinavia where much work was done were in doubt as to the results but thought that further efforts were worthwhile M Madsen ("Whooping cough" Boston M & S J 192 50 1925) the great Danish authority in his Cutler Lecture at Harvard was also optimistic but uncertain about the effects of vaccine P H Leslie and H D Gardner ("The phases of Haemophilus pertussis" J Hyg 31:423 1931) opened a new chapter in the subject when they showed that the antigenic powers of pertussis bacilli were altered by growth on artificial media and implied that organisms freshly isolated on blood agar (in Phase I) were perhaps "the only antigen for the production of active immunity in guinea pigs" L. Sauer ("Present status of preventive inoculation against whooping cough" Am J Dis Child 54 979 1937) an enthusiastic advocate of the vaccine concludes "Inoculation with potent antigen confers protection on a high precentage of young children" J J Miller Jr and H K. Faber (Immu nization against pertussis" J.A.M A. 112 1145 1939) using Phase I vaccine concluded that good protection was achieved in most cases "These observations indicate that the vaccine used conferred either complete or partial protection on the great majority of those inoculated." J J Miller critically reviews the whole problem "I think it is self-evident that active immunization against pertussis has been accomplished with certain preparations under certain con ditions" Finally H M Felton and C Y Willard ("Current status of prophy laxis by Hemophilus pertussis vaccine" J.A M.A 126 294 1944) review the literature to date and conclude that while the earlier work was doubtful re cently developed vaccines "do confer significant protection as measured by reduction in attack rate and severity of pertussis"

In summary then according to published reports the case seems conclusive in favor of the Bordet-Gengou bacillus as the cause of whooping cough How ever it seems to us that the *final* word as to exclusion of a viral etiology has not yet been said

Not everyone was willing blindly to accept the Bordet Gengou bacillus as the cause of whooping cough F Freyer in an elaborate study of the pathology of pertussis ("Ueber die pathologische Anatomie der Lungenveranderungen beim Keuchhusten" *Frankfurt Ztschr f Path* **35** 213 1927) described a case with intranuclear inclusions in the lung cells "signs of the presence of a peculiar virus" McCordock, however enumerated the points of resemblance between pertussis and known virus infections namely the interstitial pneumonia indistinguishable from that seen in influenza and measles and the encephalitis which also occurs following measles and influenza He pointed out that inclusion bodies are often associated with virus diseases and he found them in twelve of thirty five cases of whooping cough "The presence of intranuclear inclusions in the lungs in such a high percentage of our cases of pertussis and their in frequency in a variety of other childhood diseases suggest that the possible role of a filterable virus must be considered in this disease Later, at a meeting of the American Association of Pathologists (*Am J Path* **13** 644 1937) McCordock stated "To date we have demonstrated them [intranuclear inclusions in pertussis] both in our St Louis material and also in sections from other cities in about 30 per cent of all cases of pertussis examined They cannot be produced by bacteria This phase of the pertussis problem can never be solved by repeating experiments with hemophilic bacteria" A R Rich ("On the etiology and pathogenesis of whooping cough" *Bull Johns Hopkins Hosp* **51** 346 1932) also analyzes the literature on the bacillus versus a virus etiology and is unconvinced that "the Bordet Gengou bacillus represents the whole story of the etiology of whooping cough"

10 RICH A R LONG P H BROWN J H BLISS E A and HOLT L E Jr Experiments upon the cause of whooping cough *Science* **76** 330 1932

At about the time that a virus etiology was being pushed by McCordock (Ref 9) H MacDonald and E J MacDonald ("Experimental pertussis" *J Infect Dis*, **53** 328 1933) on the basis of the production of whooping cough by inoculation with cultures of the Bordet Gengou bacillus and failure to produce disease in vaccinated controls or in boys inoculated with filtrates concluded that "a filter passing virus plays no rôle in the etiology of pertussis The disease is caused by the bacillus of Bordet and Gengou Active immunity is conferred by the injection of B pertussis vaccine" As only a very few subjects were used there is some question as to the MacDonalds emphatic and sweeping conclusions J M Frawley ("A study of the virus factor in whooping cough," *J Pediat* **16** 18 1940) also failed to produce any symptoms "resembling whooping cough" in twelve children given nasal instillations of filtered washings from children with whooping cough

Rich and his colleagues report the production of a disease in chimpanzees in every way indistinguishable from whooping cough and associated with the presence of the Bordet bacilli in huge numbers in cough plates following the instillation of Bordet bacilli into the respiratory passages Filtrates of sputum from early cases of pertussis on the other hand produced only mild "febrile upper respiratory catarrhs" G S Shibley ("Etiology of whooping cough" *Proc Soc Exper Biol. & Med* **31**:576 1933) inoculated a chimpanzee with a strain of the Bordet bacillus subcultured long enough to rule out the associa

tion with a virus and produced in the animal what was regarded as typical whooping cough At autopsy *H pertussis* was recovered from bronchi and bronchioles but Shibley did not demonstrate "H pertussis like organisms embedded in cilia"

The numerous transmission experiments recorded in the literature are reviewed by Lapin (*op cit* p 43) However in evaluating these experiments one should remember that washings from influenza a disease now known to be caused by a virus have also failed to produce disease in man (M J Rosenau Experiments to determine mode of spread of influenza" J.A M A 73 311 1919) whereas reliable workers thought that they had produced influenza with instillations of the influenza bacillus

11 MILLER J J Jr The present status of immunization against pertussis California & West Med 53:25 1940

Early after the discovery of the Bordet Gengou bacillus attempts were made at treatment and prophylaxis by vaccines prepared from these organisms H N Appel and O I Bloom ("Whooping cough and its treatment" Arch Pediat 39 145 1922) give a list of the most important reports beginning in 1909 and show that variable conclusions were drawn A H Meyer M Christensen and E Sorensen ("Whooping cough vaccination" Acta paediat 4 21 1925) in Scandinavia where much work was done were in doubt as to the results but thought that further efforts were worthwhile M Madsen ("Whooping cough" Boston M & S J 192 50 1925) the great Danish authority in his Cutler Lecture at Harvard was also optimistic but uncertain about the effects of vaccine P H Leslie and H D Gardner ("The phases of Haemophilus pertussis" J Hyg 31 423 1931) opened a new chapter in the subject when they showed that the antigenic powers of pertussis bacilli were altered by growth on artificial media and implied that organisms freshly isolated on blood agar (in Phase I) were perhaps "the only antigen for the production of active immunity in guinea pigs" L. Sauer (Present status of preventive inoculation against whooping cough" Am J Dis Child 54:979 1937) an enthusiastic advocate of the vaccine concludes "Inoculation with potent antigen confers protection on a high precentage of young children" J J Miller Jr and H K Faber ("Immunization against pertussis" J.A M.A 112 1145 1939) using Phase I vaccine concluded that good protection was achieved in most cases "These observations indicate that the vaccine used conferred either complete or partial protection on the great majority of those inoculated" J J Miller critically reviews the whole problem "I think it is self evident that active immunization against pertussis has been accomplished with certain preparations under certain conditions" Finally H M Felton and C Y Willard ("Current status of prophylaxis by Hemophilus pertussis vaccine" J A M.A 126:294 1944) review the literature to date and conclude that while the earlier work was doubtful recently developed vaccines "do confer significant protection as measured by reduction in attack rate and severity of pertussis"

In summary then according to published reports the case seems conclusive in favor of the Bordet-Gengou bacillus as the cause of whooping cough However it seems to us that the *final* word as to exclusion of a viral etiology has not yet been said